STATE-RELATED QUANTITATIVE ELECTROENCEPHALOGRAPHY IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

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State-related quantitative electroencephalography in attention-deficit/hyperactivity disorder

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TABLE OF CONTENTS

Chapter 1	*General introduction*	1
Chapter 2	*Resting EEG in ADHD: developmental course and diagnostic value*	43
Chapter 3	*EEG activity before and after cognitive effort in children with ADHD*	69
Chapter 4	*State-related EEG deviances in ADHD*	103
Chapter 5	*Differential effects of pink noise on the EEG of adults with ADHD*	131
Chapter 6	*Task-related EEG deviances in adults with ADHD*	159
Chapter 7	*General discussion*	195
Nederlandstalige samenvatting		239

CHAPTER 1

GENERAL INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder that often persists across the lifespan and has a severe impact on social, academic and occupational functioning. In the past decades, quantitative electroencephalography (EEG) has frequently been used to investigate the neural correlates of ADHD. The goal of this dissertation is to gain more insights into the nature and significance of EEG deviances in ADHD. While a myriad of studies have demonstrated that behavioural and cognitive deficits in ADHD largely depend on contextual and state factors, this has hardly been addressed in EEG research. Therefore, a particular focus of this dissertation is on state-related EEG in ADHD. In this chapter, first some information is given on the characteristics of ADHD, the aetiological factors that may be involved in the disorder and the neuropsychological theories explaining ADHD deficits. Then, an overview of EEG findings in ADHD is provided and the EEG-based models that have been developed to interpret EEG deviances in ADHD are shortly reviewed. Next, the clinical implications of EEG findings in ADHD are addressed. Subsequently, some possible explanations of inconsistent EEG findings between studies are discussed. Finally, the research objectives are presented and an overview of the chapters included in this dissertation is given.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Definition

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that is characterized by a developmentally inappropriate pattern of inattention and/or hyperactivity-impulsivity. Based on criteria established by the Diagnostic and Statistical Manual of Mental Disorders- fourth edition, text revision (DSM-IV-TR, American Psychiatric Association (APA), 2000), three subtypes of ADHD are specified: (a) the predominantly inattentive type (b) the predominantly hyperactive/impulsive type, and (c) the combined type. The symptoms have to be present for at least six months and some of them must have been expressed before the age of seven. In addition, the symptoms are required to be observed in two or more settings and to cause significant impairment in social, academic or occupational functioning. The manifestation of the disorder typically fluctuates depending on contextual factors within a given setting. That is, individuals usually express less (or even no) problems when they are frequently getting rewarded for appropriate behaviour, receive consistent external stimulation, undertake interesting activities, are in a novel setting, are closely supervised, and during one-on-one interactions (APA, 2000).

All participants with ADHD in our studies received a diagnosis according to the DSM-IV-TR criteria. Meanwhile, a new edition of the DSM has been published (APA, 2013). While in the DSM-IV-TR, ADHD is categorized as a "disorder usually first diagnosed in infancy, childhood, or adolescence", in the DSM-5, it is classified as a "neurodevelopmental disorder". The diagnostic criteria for ADHD remained largely the same in the new publication, except for the substitution of subtypes by presentation specifiers that actually are highly equivalent to the prior subtypes. Further, the age criterion has been raised to having several symptoms present before the age of 12 and diagnostic criteria for adults have been adapted in the DSM-5 (APA, 2013). Research has

documented that a substantial number of children continue to meet DSM criteria for ADHD in adolescence (e.g., Barkley, Fischer, Edelbrock, & Smallish, 1990; Bussing, Mason, Bell, Porter, & Garvan, 2010) and adulthood (e.g., Klein et al., 2012; Lara et al., 2009). Yet, the prominent behavioural manifestations of hyperactivity in childhood often shift to a more subtle expression of symptoms in adulthood (e.g., Faraone, Biederman, & Mick, 2006; Kooij et al., 2010; Spencer, Biederman, & Mick, 2007).

Prevalence

The worldwide prevalence rates of ADHD across the lifespan are estimated between 5 to 7% (Willcutt, 2012). Within general population samples, the inattentive type is the most prevalent, while the combined subtype is more often represented in clinical samples (Willcutt, 2012). A higher prevalence is detected in boys than in girls, with a male-to-female ratio of 3:1 in community samples and 9:1 in clinic-referred samples (Biederman et al., 2002).

Comorbidity with other disorders

Through the lifespan, comorbidity with other psychiatric disorders and learning disabilities is high. Disorders that commonly have been found to co-occur with ADHD include oppositional defiant disorder (ODD), conduct disorder (CD), mood disorders, anxiety disorders, Tourette syndrome, autism spectrum disorder, motor incoordination, language disorders, dyslexia and dyscalculia (Biederman & Faraone, 2005; Daley, 2006; Spencer et al., 2007; Voeller, 2004).

AETIOLOGY OF ADHD

The aetiology of ADHD is considered to be complex and multifactorial, with several genetic, environmental and neurobiological factors contributing to the disorder.

Genetic factors

Genetic studies estimate the heritability of ADHD to be approximately 76% (for a review, see Faraone et al., 2005). Candidate gene studies revealed that the genes with the most consistent evidence to be associated with ADHD are the dopamine D4 and D5 receptors, the dopamine active transporter 1, the serotonin transporter 5HTT, the serotonin 1B receptor and the synaptosomal-associated protein 25 (for reviews, see Gizer, Ficks, & Waldman, 2009 and Thapar, Cooper, Eyre, & Langley, 2013). In addition, the latrophilin 3 and cadherin 13 genes have been related to adults with persistent ADHD (for a review, see Franke et al., 2012). Although support has been found for (variants of) these genes to be involved in ADHD, so far no significant genome-wide associations with ADHD could be identified (for a review, see Ashmore & Cheng, 2013; for a meta-analysis, see Neale et al., 2010). This suggests that the impact of individual genes on the aetiology of ADHD is small or that rare types of genetic variants explain the heritability of the disorder (Ashmore & Cheng, 2013; Neale et al., 2010).

Environmental factors

Several environmental factors have been linked to the aetiology of ADHD. The most frequently reported risk factors are maternal smoking, alcohol and substance abuse during pregnancy, prematurity and low birth weight, childhood illnesses, exposure to environmental toxins, low family income, low parental education, disturbances in family functioning, disrupted parent-child relations and exposure to maternal

psychopathology (e.g., Biederman et al., 1995; Biederman & Faraone, 2005; Cortese, 2012; Nigg, Nikolas, Knottnerus, Cavanagh, & Friderici, 2010; Thapar, Cooper, Jefferies, & Stergiakouli, 2012; Thapar et al., 2013). However, none of these factors have been proven to play a definite causal role in ADHD (Cortese, Faraone, & Sergeant, 2012). Moreover, the gene-environment interaction also seems to be important in the aetiology of ADHD (Nigg, 2012; Pennington et al., 2009).

Neurobiological factors

Neuroimaging studies exploring the neurobiological profile of ADHD have identified altered structure and function in several brain regions, including fronto-striatal, fronto-parietal, fronto-cerebellar neural networks, as well as lateral orbitofrontal-ventromedial networks (e.g., Arnsten & Rubia, 2012; Cubillo, Halari, Smith, Taylor, & Rubia, 2012). Functional abnormalities are not only detected in isolated brain regions, also the functional interconnectivity between regions appears to be impaired in ADHD (e.g., Purper-Ouakil, Ramoz, Lepagnol-Bestel, Gorwood, & Simonneau, 2011; Rubia, Cubillo, Woolley, Brammer, & Smith, 2010).

NEUROPSYCHOLOGICAL THEORIES ON THE AETIOLOGY OF ADHD

Several theoretical models have been developed to provide a comprehensive account of the behavioural and cognitive deficits associated with ADHD. The most influential and well-investigated accounts are outlined below.

Executive dysfunction account

In the executive dysfunction theory (Barkley, 1997), a deficiency in executive functioning is proposed to underpin ADHD. Executive functions refer to a set of top-down cognitive processes that are coordinated in order to achieve self-control and goal-

directed behaviour (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006). According to the model, deficient inhibitory control is the primary deficit in ADHD, in turn contaminating other executive functions (i.e., working memory, self-regulation of affect, motivation and arousal, internalization of speech, and reconstitution) (Barkley, 1997).

Although a few meta-analyses have confirmed that individuals with ADHD show impairments in several domains of executive functioning, effect sizes were moderate and executive dysfunction was not found to be a characteristic of all individuals with ADHD (Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Moreover, while in this theory, executive dysfunction tends to be regarded as a fixed deficit in ADHD, this appears to disaccord with research demonstrating executive functions themselves to be dynamic processes and performance on executive tasks in ADHD to vary across states and settings (e.g., Nigg, & Casey, 2005; Shiels et al., 2008).

In line with findings demonstrating the dynamic nature of impairment in ADHD, alternative theoretical accounts have been developed, emphasizing the role of contextual and state factors in defining deficits (Sonuga-Barke, Wiersema, van der Meere, & Roeyers, 2010a).

Delay aversion account

In the delay aversion theory (Sonuga-Barke, Taylor, Sembi, & Smith, 1992), the context dependent nature of ADHD is defined from a motivational perspective. In specific, the model postulates that an impaired signalling of future rewards underlies deficits in ADHD, resulting in a drive for immediate rewards (Sonuga-Barke et al., 2010a). This is particularly expressed in a preference for instant over delayed rewards (Sonuga-Barke et al., 1992) and a smaller investment of time and effort in long and boring tasks to avoid or escape from delay (Sonuga-Barke, De Houwer, De Ruiter, Azensten, & Holland, 2004).

Research findings support the notion that delay aversion is implicated in ADHD but, as is the case for weaknesses in executive functioning, it is neither a necessary nor a sufficient cause of ADHD in all individuals (Sonuga-Barke, Sergeant, Nigg, & Willcutt, 2008).

State regulation account

The state regulation account (Sergeant, 2005; van der Meere, 2005) found its origin in the cognitive-energetic model of Sanders (1983), which postulates that human processing capacity is determined by the interplay between processing stages (i.e., encoding, feature extraction, response selection and response execution) and energetic state factors (i.e., arousal, activation and effort). The model accentuates that context factors largely account for the variable expression of deficits in ADHD and that impairments in ADHD result from a deficiency to regulate energetic state in challenging suboptimal conditions (Sonuga-Barke et al., 2010a).

Research into this theoretical construct has mainly focussed on evaluating task performance while manipulating presentation rate of stimuli, as this is believed to affect activation level (Johnson, Wiersema, & Kuntsi, 2009). In accordance with the model, numerous studies using a large variety of tasks have demonstrated worse performance in children with ADHD in tasks with slow and fast event rates compared to moderate event rates (e.g., Brown & Vickers, 2004; Leung, Leung, & Tang, 2000; for a meta-analysis, see Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012; Rubia, Taylor, Taylor, & Sergeant, 1999; Scheres, Oosterlaan, & Sergeant, 2001; Wiersema, van der Meere, Antrop, & Roeyers, 2006a; Wiersema, van der Meere, Roeyers, Van Coster, & Baeyens, 2006b). Further support for the notion of state regulation deficits in slow event rate conditions can be derived from cardiac response and electrophysiological studies, which have described difficulties with the regulation of effort allocation in ADHD (Börger & van der Meere, 2000; Wiersema et al., 2006a,b).

From single core deficit to multiple pathways

Although the aforementioned single core deficit models each provide a valuable contribution to explaining some of the problems related to ADHD, none of the theoretical constructs are successful in accounting for the entire spectrum of deficits in ADHD (e.g., Sonuga-Barke, 2002). Consequently, it was recognised that ADHD is a very heterogeneous disorder with multiple causal and developmental pathways (e.g., Nigg, 2005a; Sonuga-Barke, 2002; Sonuga-Barke, Bitsakou, & Thompson, 2010b).

ELECTROENCEPHALOGRAPHY

Electroencephalographic measurements were among the first to be used to investigate the neural correlates of ADHD (Loo & Barkley, 2005) and have been used as such for over 40 years.

Electroencephalography (EEG) is a non-invasive imaging technique to monitor brain electrical activity (Teplan, 2002). EEG measures voltage fluctuations on the scalp, resulting from synchronous activity of large collections of neurons in the brain (Başar & Güntekin, 2008). The procedure offers excellent temporal but rather poor spatial resolution because electrical activity recorded from the scalp is not always directly mapped to a specific underlying brain structure and may be contaminated by various electrical artifacts (Loo & Barkley, 2005).

EEG activity consists of oscillations at different frequencies (i.e., number of oscillations within a given time period), which are generally categorised in different frequency ranges: delta (<4 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (13-25 Hz), and gamma (25-50 Hz) (Loo & Makeig, 2012). In ADHD research, the most commonly studied frequency bands are the theta, alpha and beta band. In addition, the theta/beta ratio (TBR), which reflects the proportion of EEG activity in the theta to that in the beta frequency band, is well-investigated in ADHD.

EEG FINDINGS IN ADHD

Most EEG studies in ADHD have evaluated brain wave activity under resting state conditions with either eyes closed or eyes open. The majority of them focussed on children, while only a few studies examined EEG activity in adolescents. As for adults, there has been a growing number of publications in recent years.

Across the lifespan, the most consistent findings in both eyes closed and eyes open resting conditions refer to increased theta activity and/or an enhanced TBR in ADHD (see Barry & Clarke, 2009 and Barry, Clarke, & Johnstone, 2003 for reviews; Clarke et al., 2011; Dupuy, Clarke, Barry, McCarthy, & Selikowitz, 2011; Dupuy, Barry, Clarke, McCarthy, & Selikowitz, 2013; González-Castro, Rodríguez, López, Cueli, & Álvarez, 2013; Koehler et al., 2009; Lansbergen, Arns, van Dongen-Boomsma, Spronk, & Buitelaar, 2011; Loo et al., 2010; Shi et al., 2012; Woltering, Jung, Liu, & Tannock, 2012). Yet, several studies were not able to invariably replicate these findings (Coolidge, Starkey, & Cahill, 2007; Liechti et al., 2013; Loo et al., 2009, 2013; Nazari, Wallois, Aarabi, & Berquin, 2011; Ogrim, Kropotov, & Hestad, 2012; Poil et al., 2014; Swartwood, Swartwood, Lubar, & Timmermann, 2003; van Dongen-Boomsma et al., 2010), which questions the robustness of these deviances characterizing individuals with ADHD. Additionally, some recent studies established that enhanced theta or TBR is only apparent in about 20 to 60% of children with ADHD (Arns, Drinkenburg, & Kenemans, 2012; Clarke et al., 2011; Ogrim et al., 2012). Moreover, theta power (Clarke et al., 2011) and TBR (Loo et al., 2013) can even be reduced in some individuals with ADHD. EEG findings regarding brain wave activity in the faster frequency bands appear to be even more mixed. That is, while some studies have documented decreased power in the beta band in ADHD (Clarke, Barry, McCarthy, & Selikowitz, 1998; Clarke, Barry, McCarthy, & Selikowitz, 2002; Clarke et al., 2003a, 2008; Dupuy et al., 2011; Hermens et al., 2004; Shi et al., 2012), others were not able to distinguish groups based on beta power (Bresnahan & Barry, 2002; Hobbs, Clarke, Barry, McCarthy, & Selikowitz, 2007;

Koehler et al., 2009; Liechti et al., 2013; Loo et al., 2010, van Dongen-Boomsma et al., 2010). In addition, a few studies have even reported increased beta power in (a subgroup of) individuals with ADHD (Chabot & Serfontein, 1996; Clarke et al., 1998; Clarke, Barry, McCarthy, & Selikowitz, 2001a; Clarke et al., 2008; Loo et al., 2010; Poil et al., 2014). Likewise, alpha power has often been documented to be reduced in individuals with ADHD (Barry, Clarke, Johnstone, McCarthy, & Selikowitz, 2009; Clarke et al., 1998; Clarke, Barry, McCarthy, & Selikowitz, 2002a; Clarke et al., 2003a; Dupuy et al., 2011; Loo et al., 2009; Woltering et al., 2012), but has also been found to be increased (Chabot & Serfontein, 1996; Clarke et al., 2011; Koehler et al., 2009), or of an equal magnitude to that of typically developing individuals (Hobbs et al., 2007; Loo et al., 2010; Shi et al., 2012; van Dongen-Boomsma et al., 2010).

Fewer studies have investigated EEG activity during task performance in ADHD. Most of them are conducted in children, while only a few have addressed an adult sample. Whereas often similar theta or TBR deviances as in resting conditions were revealed in children with ADHD during a variety of tasks (El-Sayed, Larsson, Persson, & Rydelius, 2002; Janzen, Graap, Stephanson, Marshall, & Fitzsimmons, 1995; Mann, Lubar, Zimmerman, Miller, & Muenchen, 1992; Monastra et al., 1999; Monastra, Lubar, & Linden, 2001), this was not confirmed by all studies (Nazari et al., 2011; Swartwood et al., 2003). Moreover, deviances in alpha power have also been described in children with ADHD during execution of various tasks (Swartwood et al., 2003). The literature on task-related EEG activity in adults is even more inconsistent. Monastra and colleagues (1999) reported elevated TBR in adults with ADHD in several tasks. Further, one study documented elevated theta power during a continuous performance task (CPT), be it only at the end of the task (Rasey, Craig, & Lubar, 1999). Other studies could not detect this and reported either an elevation (White, Hutchens, & Lubar, 2005) or a reduction (Loo et al., 2009) in alpha power during CPT in adults with ADHD. Moreover, deviances in alpha power in ADHD appeared to be task-dependent (White et al., 2005). Further,

alteration in task-related alpha (Loo et al., 2009) or beta power (Rasey et al., 1999) in ADHD has been related to time-on-task effects.

EEG-BASED MODELS OF ADHD

In an attempt to explain the most common EEG deficits (i.e., aberrant theta and TBR) associated with ADHD, several theoretical models have been developed. Remarkably, EEG studies have hardly referred to well-established existing neuropsychological models of ADHD to explain EEG deviances, although several EEG-based models appear to rely on concepts that have also been accentuated in those theoretical constructs.

Maturational lag

The maturational lag model suggests that the typically found elevated theta power and TBR, as well as the often found reduced beta power in ADHD might reflect a lag or delay in cortical development (Clarke et al., 1998; Lazzaro et al., 1998; Mann et al., 1992; Satterfield, Schell, Backs, & Hidaka, 1984). In the model, it is proposed that individuals with ADHD are underdeveloped for their age and act in a way that would be considered normal for a younger age group (Kinsbourne, 1973). For this account to be accurate, EEG activity of individuals with ADHD should be similar to that of typically developing younger age groups (Clarke et al., 2008). Indeed, as for EEG maturation, a massive body of literature has indicated that power in the slower frequency bands (e.g., theta) reduces with age, whereas power in the faster frequency bands (e.g., beta) increases (see Barrigo-Paulino, Flores, & Gomez, 2011). Also, a decrease in TBR has been documented with maturation (Monastra et al., 1999). However, several EEG studies in adults with ADHD have established EEG deviances similar to those in children with ADHD (Bresnahan & Barry, 2002; Clarke et al., 2008; Woltering et al., 2012), which

argues against the maturational lag model as conceptually, it is not likely to have a maturational lag that persists into adulthood (Barry et al., 2003).

Underarousal

According to the underarousal model, theta, beta and TBR deviances in ADHD are accounted for by cortical underarousal (Lubar, 1991; Mann et al., 1992). The model was founded by Lubar (1991), who linked findings of reduced skin conductance levels (representing central nervous system (CNS) underarousal) in ADHD (Satterfield & Dawson, 1971) with findings of EEG power shifts from dominant theta and alpha to dominant beta power when going from resting to active states (Jasper, Soloman & Bradley, 1938). In the model, it is hypothesized that children with ADHD are chronically underaroused, which is expressed in increased theta power with a reciprocal reduction of beta power (Lubar, 1991). However, a problem with this model explaining EEG deviances refers to the fact that the association between low skin conductance level (SCL) and enhanced TBR was based on a theoretical rationale, which was not specifically validated (Barry et al., 2009). Recent studies have demonstrated that while children with ADHD exhibited both reduced SCL and enhanced TBR, no correlations were found between those measures (Barry et al., 2009; Clarke et al., 2013), which challenges the role of theta and beta activity as markers of arousal. Instead, it was denoted that power in the alpha frequency band is primarily related to arousal (Barry, Clarke, Johnstone, Magee, & Rushby, 2007; Barry et al., 2009). Consequently, while researchers currently are more cautious in attributing theta and TBR deviances to deficiencies in arousal in ADHD, the concept of arousal is nowadays often used to explain aberrant alpha power (e.g., Fonseca, Tedrus, Bianchini, & Silva, 2013; Loo et al., 2009; van Dongen-Boomsma et al., 2010).

The lack of finding an association between TBR and SCL has led to a reframing of TBR in terms of reflecting impaired activation and a processing deficit in ADHD (Barry et

al., 2009, Clarke et al., 2013). Accordingly, a few studies have reported that performance measures during task execution are related to theta (Hermens et al., 2005; Swartwood et al., 2003) or beta activity (Loo, Hopfer, Teale, & Reite, 2004) or TBR (Loo et al., 2013; van Dongen-Boomsma et al., 2010) but see Ogrim et al., 2012. Yet, it should be noted that the specific nature of the performance measures (i.e., reaction time, errors, ...) that are associated with the EEG parameters differs across studies.

Noteworthy, over the past few decades, the concepts of arousal and/or activation have been used by several theoretical constructs to explain the behavioural and cognitive deficits associated with ADHD. According to the optimal stimulation theory (Zentall & Zentall, 1983), the engagement in ADHD behaviours is a homeostatic mechanism that functions to compensate for a state of underarousal. Further, as aforementioned, the concepts of arousal and activation are key components of the state regulation account of ADHD (Sergeant, 2005; van der Meere, 2005). Yet in that model, the dynamic nature of deficits in ADHD is emphasized, a notion which so far appears to be less incorporated in EEG research.

Reduced top-down control

As slow EEG frequencies are suggested to arise from subcortical structures, while fast frequencies originate from thalamo-cortical and cortico-cortical circuits (Schutter & Knyazev, 2012), it has been suggested that increased slow to fast wave ratios (i.e., TBR) reflect reduced cortical control over subcortical structures (Schutter, Leitner, Kenemans, & van Honk, 2006; Knyazev, 2007). In this framework it is postulated that slow waves are associated with lower motivational systems, which bias the system to response activation, and that fast waves are linked to higher cognitive systems, which promote inhibition (Schutter et al., 2006). Hence, TBR is thought to represent reduced control over approach drive, which translates into a deficiency in inhibition (Putman, van Peer, Maimari, & van der Werff, 2010). The relation between TBR and poor inhibition is

consistent with findings of associations between TBR and risky decision-taking (Massar, Kenemans, & Schutter, 2013; Schutter & van Honk, 2005), and decreased self-reported levels of attentional control as well as decreased expression-specific response bias to faces in an emotional go/no-go task in typically developing adults (Putman et al., 2010). In an adult ADHD group, the notion of TBR reflecting weaknesses in inhibition has been confirmed by the finding of a positive correlation between TBR and reaction time during a stop signal task in ADHD (van Dongen-Boomsma et al., 2010), in which reaction time was interpreted as a measure of impulsivity as error rates during the task were high (but see Loo et al., 2013 for counter case).

Interestingly, again a parallel can be drawn with a dominant explanatory model of ADHD, namely the above mentioned executive dysfunction theory of ADHD, which proposes that ADHD deficits originate from impairments in executive functions (i.e., top-down processes), especially in response inhibition (Barkley, 1997).

CLINICAL IMPLICATIONS OF EEG FINDINGS IN ADHD

Diagnostic use of EEG

As up to date, diagnosis of ADHD is based on the subjective assessment of behavioural symptoms and impairment, objective biomarkers would provide a valuable adds-on (Liechti et al., 2013). In concordance with the frequently found abnormalities in TBR and theta power across a number of resting EEG studies, the potential of these EEG parameters as diagnostic biomarkers has been proposed (Monastra et al., 2001; Snyder et al., 2008). In order to be considered as reliable indicators of the disorder, EEG deviances should be meaningfully associated with and specific for ADHD (Boksa, 2013). Several studies have investigated the accuracy of EEG parameters in classifying individuals according to their diagnostic status. While earlier studies have documented

high sensitivity (90% and 87%) and specificity (both 94%) rates for TBR (Monastra et al., 2001; Snyder et al., 2008), the most recent studies have established an insufficient overall accuracy for TBR (40.3% and 58%) as well as for theta power (46.8% and 63%) in distinguishing individuals with ADHD from a control group (Liechti et al., 2013; Ogrim et al., 2012). Moreover, increased theta appears to be pathognomonic to a number of other disorders such as epilepsy, bipolar disorder, substance abuse, dementia, alcoholism and schizophrenia (Coutin-Churchman et al., 2003). Besides, given that the behavioural and cognitive deficits in ADHD are well-known to fluctuate with respect to environmental context (e.g., Antrop et al., 2006; Metin et al., 2012), it is not unlikely that EEG deviances in ADHD are context or state dependent as well, which would raise an additional difficulty in the potential use of quantitative EEG as a diagnostic tool.

Altogether, these findings suggest that traditional quantitative EEG measures are not feasible to be used for diagnostic purposes. However, recently the U.S. Food and Drug Administration approved the marketing of a medical device that registers TBR in order to assist in assessing ADHD in children and adolescents (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm360811.htm).

Prognostic use of EEG

Nowadays, there is an increasing interest in using quantitative EEG as a prognostic instrument to differentiate subgroups in their response to various treatments (Arns et al., 2012). Whereas the traditional diagnostic use of EEG assumes homogeneity among individuals with ADHD, in the prognostic approach, heterogeneity is stressed. A few studies have illustrated that an EEG pattern characterized by excessive (frontal) theta is a good indicator for clinically significant treatment response to stimulant medication (Arns, Gunkelman, Breteler, & Spronk, 2008; Ogrim et al., 2014; Satterfield, Dennis, Cantwell, Lesser, & Posodin, 1972; Suffin & Emory, 1995), whereas individuals with slow alpha frequency (Arns et al., 2008) or excessive alpha power (Suffin & Emory,

1995) are less responsive to stimulants. Although these findings suggest that EEG may be of value for prognostic purposes, more studies are needed to confirm this.

Treatment use of EEG

The repeatedly observed increased theta, decreased beta and enhanced TBR in ADHD have been used as a rationale for EEG biofeedback treatment, also known as neurofeedback (Loo & Makeig, 2012). This EEG based treatment relies on the principles of operant conditioning and aims to train EEG activity in the desired direction (i.e., reduction of theta and enhancement of beta power) in order to diminish ADHD symptoms (Heinrich, Gevensleben, & Strehl, 2007). While neurofeedback seems to be a promising approach in the treatment of ADHD (for a meta-analysis, see Arns, de Ridder, Strehl, Breteler, & Coenen, 2009; for a review, see Gevensleben, Rothenberger, Moll, & Heinrich, 2012), insights into the core mechanisms of action, moderators and mediators are limited (Arns, Heinrich, & Strehl, 2014; Gevensleben et al., 2014). Also, it is important to note that, although some recent studies addressed some of these shortcomings, a lot of neurofeedback studies suffer from methodological issues such as small sample sizes, and lack of an adequate control group or randomization (Loo & Makeig, 2012), which hampers formulating firm conclusions regarding the efficacy of the therapy. Besides, lately the justification of the rationale for neurofeedback has been challenged, since the consistency of the typically observed deviances characterizing the EEG profile of ADHD has come into question, as several studies failed to find these abnormalities (Coolidge et al., 2007; Liechti et al., 2013; Loo et al., 2009, 2013; Nazari et al., 2011; Ogrim et al., 2012; Poil et al., 2014; Swartwood et al., 2003; van Dongen-Boomsma et al., 2010). With respect to this, it has been hypothesized that neurofeedback training is not a matter of fixing EEG deficits, yet rather implicates training compensatory mechanisms (Arns et al., 2014; Gevensleben et al., 2012).

In all, there are still a lot of open questions regarding neurofeedback and the hypothesized underlying EEG abnormalities that are addressed by the training.

INCONSISTENCIES IN EEG FINDINGS ACROSS STUDIES

Though a large body of literature refers to deviances in theta power and TBR in ADHD, also an increasing amount of studies fail to find these abnormalities. Various factors may have contributed to these apparent discrepant findings between studies.

EEG instrumentation, recording and quantification procedures

First, variation in EEG instrumentation across studies can impede comparison between datasets (Loo & Makeig, 2012). Furthermore, studies differ in EEG data processing and methodology used for analyses (Arns, Conners, & Kraemer, 2013; van Dongen-Boomsma et al., 2010). For example, studies vary in filtering techniques, deartifacting methods, duration of epochs that are averaged, number and combination of electrodes used to analyse EEG activity, definition of the borders of the frequency ranges that are investigated, statistical procedures to conduct analyses and so on.

Sample characteristics

Control samples. It is not always clear which cut-off score on ADHD related questionnaires (e.g., below clinical or below subclinical scores) was used to incorporate individuals in the control groups of studies. Also, EEG studies in ADHD have uncommonly explicitly documented whether children with psychiatric or learning disorders were included in their control groups.

ADHD samples. ADHD comprises a heterogeneous clinical expression with different behavioural subtypes (i.e., inattentive subtype, hyperactive/impulsive subtype,

combined subtype) and often comorbid disorders (i.e., oppositional defiant disorder, conduct disorder, antisocial disorders, mood disorders, anxiety disorders, learning disorders, substance abuse) are rather a rule than an exception (Biederman, 2005). These sample characteristics may vary across EEG studies and may possibly mediate EEG deviances in ADHD.

Regarding the differentiation in EEG activity between ADHD subtypes, disparate findings have been reported. While in most studies individuals with ADHD inattentive subtype (ADHD-I) have been documented to demonstrate an in-between pattern of abnormalities between ADHD combined subtype (ADHD-C) and control subjects (Clarke et al., 1998; Clarke et al., 2001b; Dupuy et al., 2011), in others no differences between subtypes (Monastra et al., 2001; Hermens et al., 2004; Loo et al., 2010) or greater deviances in ADHD-I compared to ADHD-C (Loo et al., 2010) have been described.

Very few studies have been devoted to the impact of comorbid disorders on EEG deviances in ADHD. As for comorbid oppositional defiant disorder (ODD) and conduct disorder (CD), one study has documented that comorbidity with ODD/CD possibly has a strengthening effect on TBR deviance in children with ADHD (Loo et al., 2013), while another study did not detect this and instead reported more pronounced focal theta abnormalities in an ADHD only group than in an ADHD group with comorbid ODD/CD (Clarke, Barry, McCarthy, & Selikowitz, 2002b). Regarding comorbid depressive disorder, this was indicated to lower deviance in TBR in ADHD (Loo et al., 2013).

Further, there is a large variety in gender proportion across EEG studies. The majority of studies included both males and females in their samples, though with various male to female ratios (e.g., Ogrim et al., 2012; Loo et al., 2009), or incorporated only males (e.g., Clarke et al., 2008), while very few studies focussed on females only (e.g., Dupuy et al., 2011). Research suggests differences in EEG deviances between males and females with ADHD (for a review, see Dupuy et al., 2013). Even so, increased slow wave activity and/or an elevated TBR have been detected in both studies

evaluating only males (e.g., Clarke et al., 2008) and only females (e.g., Dupuy et al., 2011), which seems to confirm that the typically found EEG deviances in ADHD are exhibited in both sexes.

Across studies, medication use of the participants with ADHD in daily life also differs, with some studies investigating medication naïve patients (e.g., Clarke et al., 2008), while others examining both individuals who are on and off medication in daily life (e.g., Shi et al., 2012). The use of stimulants has been shown to decrease theta power (Loo, Teale, & Reite, 1999; Clarke et al., 2003b; Clarke, Barry, McCarthy, Selikowitz, & Johnstone, 2007) and TBR (Clarke et al., 2002b). While most studies properly control for medication effects, little is known about the long-term effects of medication use on EEG activity.

Differences in experimental design

Another factor of variance between studies refers to the condition in which EEG was recorded. So far, most EEG studies in ADHD have evaluated resting EEG with either eyes closed or eyes open, whereas only a few of them have included both conditions (Fonseca et al., 2013; Lansbergen et al., 2011; Liechti et al., 2013; Loo et al., 2009, 2010, 2013; van Dongen-Boomsma et al., 2010; Woltering et al., 2012). Interestingly, some studies addressing both resting conditions have reported deviances in TBR (Lansbergen et al., 2011; Loo et al., 2013) in ADHD in the eyes closed but not in the eyes open condition. Also, studies have demonstrated reduced alpha suppression to opening of the eyes (Fonseca et al., 2013; Loo et al., 2010; Woltering et al., 2012) or greater theta power increase to closing of the eyes (Liechti et al., 2013) in ADHD. Opening of the eyes is a well-known procedure to generate an increase in arousal (Barry et al., 2007; Hüfner et al., 2009). Hence, these findings appear to indicate the implication of state-related factors in EEG abnormalities in ADHD.

This notion is further supported by studies reporting deficiencies in the transition between a resting and an active state in ADHD. That is, increased alpha power (Nazari et al., 2011) and reduced attenuation of beta power (Loo et al., 2009) have been documented in ADHD when making the transition from an eyes open resting condition to task performance.

Further evidence for the dynamic nature of EEG divergence in ADHD comes from a few studies addressing several tasks when evaluating on-task EEG activity. There, it is striking that the expression of EEG differences between groups largely depends on the tasks that are being performed. In particular, alpha power was found to be decreased in children with ADHD in a reading task, while increased in a coding task and normal in drawing and listening tasks as well as in the Raven's Progressive Matrices task (Swartwood et al., 2003). Likewise, alpha power was observed to be enhanced in adults with ADHD during CPT performance but not during the execution of the Wisconsin Card Sorting Task and the Paced Auditory Serial Addition Task (White et al., 2005).

In all, studies including different conditions when evaluating EEG activity suggest that EEG deviances in ADHD may fluctuate across states and settings. Remarkably, so far this conception has hardly been infiltrated in the EEG literature, although it appears to be a crucial fact to better understand EEG deviances and their significance in ADHD. Besides, it should be noted that multiple studies have already disclosed dynamic, context-dependent variations in behavioural and performance deficits in ADHD. More specifically, deficits in individuals with ADHD have been found to be more pronounced in situations with low stimulation - as mostly investigated by including slow presentation rate of stimuli during tasks - (for a meta-analysis, see Metin et al., 2012; Wiersema et al., 2006a,b), long task duration (Toplak & Tannock, 2005), delay (Antrop et al., 2006), absence of supervision (Power, 1992) and a lack of structure (Zentall & Leib, 1985) and reinforcement (for a review, see Luman, Oosterlaan, & Sergeant, 2005). Altogether, the behaviour of individuals with ADHD aggravates and their performance deteriorates in

situations in which high demands are placed on self-regulatory, motivational and information processing skills (Imeraj et al., 2013; Nigg, 2005b). Consistent with this, as aforementioned, a number of theoretical accounts of ADHD have emphasized the role of contextual and state dependent factors in ADHD deficits (i.e., delay aversion model, state regulation model). From all this it results that translating the insights regarding the context and state dependent fluctuations of deviances in ADHD from behavioural and performance studies into EEG literature would be a valuable approach to increase knowledge on (the meaning of) EEG deviances in ADHD.

RESEARCH OBJECTIVES OF THE DOCTORAL DISSERTATION

While numerous studies have described enhanced theta and increased TBR in ADHD, these EEG deviances appear to be not as consistent as assumed, since several recent studies were not able to detect these abnormalities. Moreover, findings in the alpha and beta frequencies seem to be even more ambiguous. Various factors may underlie these inconsistent findings across studies, including contextual and state-related factors. Whereas it is well-established that the behavioural and cognitive deficits associated with ADHD fluctuate in response to a diversity of contextual and state factors, this dynamic feature of deficits has hardly been addressed in quantitative EEG studies. Yet, findings of studies that compare EEG activity between several conditions suggest possible context/state dependent variations in EEG deviances in ADHD. This calls for further research, especially in view of the increasing interest to integrate EEG into clinical practice for diagnostic and treatment purposes.

Therefore, the first aim of this doctoral dissertation is to gain more insights into the stability of EEG deviances in ADHD across conditions and the influence of dynamic (i.e., contextual, state) factors on EEG in ADHD. This is directly related to the second goal of this dissertation, which is to improve knowledge on the functional significance of

aberrant EEG activity in ADHD. EEG-based models have explained deviances in theta power and TBR in ADHD in terms of either maturational delay, cortical underarousal, deficiencies in activation or reduced top-down control. These hypotheses will be investigated and integrated with insights from several well-established neuropsychological accounts of ADHD.

Not only theta power and TBR, which show the strongest evidence to distinguish individuals with ADHD from typically developing individuals, will be investigated, also alpha and beta power will be addressed. Alpha power will be examined because activity in the alpha band has been postulated to reflect arousal and deficits in (regulation of) arousal have often been associated with ADHD. Regarding beta activity, this has frequently been related to activation or compensatory effort, which have also been proposed to deviate in ADHD.

OVERVIEW OF THE CHAPTERS

In the following chapters, five empirical studies are reported that were based on three different samples, including typically developing children and adults as well as children and adults with ADHD.

In *chapter 2,* a cross sectional study in children and adults with and without ADHD is described in which three minutes eyes closed resting EEG was compared across diagnostic status and across age groups. The first aim of the study was to determine whether similar possible EEG deviances in ADHD were present across age groups, thereby addressing the suggestion of a maturational delay underlying EEG deviances in ADHD. The second goal of the study was to investigate whether it would be possible to accurately classify the diagnostic status of individuals by means of EEG measures.

In c*hapter 3,* three minutes eyes closed resting EEG before and after cognitive effort were compared between children with ADHD and typically developing children.

So far, EEG studies in ADHD focussed on evaluating EEG either at the start or at the end of a laboratory visit, respectively before and after cognitive effort. A few studies in typically developing individuals denoted that resting EEG activity may change after task execution (Smit, Eling, & Coenen, 2004; Smit, Eling, Hopman, & Coenen, 2005; Tanaka et al., 2012), hence demonstrating that resting EEG may be affected by contextual factors. Accordingly, the registration of EEG activity both before and after task execution enabled us to examine the stability of possible EEG divergence between groups across conditions and addressed the state-dependent nature of deviances in ADHD related to intervening cognitive effort.

Chapter 4 describes a study that was designed to compare three minutes resting EEG activity with eyes closed and eyes open between children with and without ADHD. As opening of the eyes is associated with a change in cortical arousal state (Barry et al., 2007), we addressed the hypothesis of deficiencies in cortical arousal in ADHD in this chapter. In particular, the study informed us whether possible deviances in ADHD were stable across different arousal states and to what extent they depended on an arousal modification.

In *chapter 5* we elaborated on the notion of possible arousal dysfunction in ADHD, which has been implicated in several theoretical models of ADHD. In the Moderate Brain Arousal model it is predicted that presenting external environmental white or pink noise modulates neuronal noise and accordingly increases arousal level (Söderlund, Sikström, & Smart, 2007). While a few studies already documented on the positive impact of noise on cognitive performance in children with attention problems (Söderlund et al., 2007; Söderlund, Sikström, Loftesnes, & Sonuga-Barke, 2010), so far the neural correlates of noise exposure have not been investigated. In this study, three minutes eyes closed resting EEG was compared with three minutes eyes closed resting EEG with exposure to pink noise in adults with ADHD and typically developing adults. It

was investigated whether the administration of noise would produce different changes in EEG activity in adults with ADHD compared to adults without ADHD.

In *chapter 6,* task-related deviances in quantitative EEG activity were investigated in adults with ADHD compared to typically developing adults. It was examined whether EEG abnormalities in ADHD might be related to a suboptimal energetic state or impairment in executive control, hence addressing the hypotheses of aberrant EEG activity representing respectively impaired activation state (Barry et al., 2009) and top-down control (Schutter et al., 2006). Therefore, EEG was evaluated during performance on a task inducing a low activation level and a task tapping top-down executive control.

Finally, *chapter 7* comprises an integrated overview and general discussion of the main findings of this dissertation. Then, theoretical and clinical implications of the findings are discussed. Further, attention is drawn to the limitations of the studies. Also, some recommendations for future research are outlined.

Important to note is that this dissertation consists of several research papers, which have been published, are currently under editorial review or have been submitted for publication. Therefore, each chapter is self-contained and there can be considerable overlap between the chapters.

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CHAPTER 2

RESTING EEG IN ADHD: DEVELOPMENTAL COURSE AND DIAGNOSTIC VALUE[1]

ABSTRACT

Objective: This study investigated electroencephalographic (EEG) activity and its developmental course in attention-deficit/hyperactivity disorder (ADHD) throughout the lifespan, as well as the accuracy of EEG parameters in distinguishing ADHD patients from typically developing individuals. **Methods:** Three minutes eyes closed resting EEG was compared between 62 individuals with ADHD (36 children, 26 adults) and 55 typically developing individuals (30 children, 25 adults). **Results:** EEG activity and maturation did not differ between individuals with ADHD and typically developing individuals. However, despite comparable developmental course between clinical groups, persistent elevated theta/beta ratio and reduced relative beta power were observed in the ADHD inattentive subtype compared to the ADHD combined subtype and controls across the lifespan. Therefore, a maturational deviation rather than a maturational delay may underlie a subgroup of ADHD. EEG based classification failed for ADHD but proved successful for age. **Conclusions:** These findings emphasize heterogeneity in ADHD throughout the lifespan and question clinical utility of conventional EEG approaches for diagnostic purposes in ADHD.

[1] Based on Buyck, I., & Wiersema, J.R. (2014). Resting electroencephalogram in attention deficit hyperactivity disorder: Developmental course and diagnostic value. *Psychiatry Research.* Advance online publication. doi: 10.1016/j.psychres.2013.12.055

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioural disorder with a childhood onset that often persists into adulthood (for a review, see Spencer, Biederman, & Mick, 2007) and is characterized by developmentally inappropriate symptoms of inattention and/or hyperactivity/impulsivity, resulting in impairment in multiple life domains (APA, 2000). The worldwide prevalence of ADHD is estimated between 5% and 7% (Willcutt, 2012).

Much effort has been devoted to laying out clinical recommendations for diagnosing ADHD, which relies on the assessment of behavioural symptoms and functional impairment (Seixas, Weiss, & Muller, 2012). Still, more objective diagnostic procedures would provide a valuable supplement. To this end, brain-based approaches seem promising, since neuroimaging studies suggest that disturbances in brain structure and function are related to overt behavioural manifestations of ADHD (Williams, Tsang, Clarke, & Kohn, 2010).

In the last decades, resting state electroencephalographic (EEG) measures have been widely used to document underlying neurophysiological dysfunction in ADHD. Although most EEG studies focus on children, there is a growing interest in adults with ADHD. The most robust findings in individuals with ADHD across the lifespan in eyes closed as well as eyes open resting state conditions are increased theta activity and/or an elevated proportion of slower to faster frequencies in the brain, as reflected in theta/beta ratio (TBR), particularly apparent at frontocentral sites (for a review, see Barry, Clarke, & Johnstone, 2003; e.g., Clarke et al., 2011b; Shi et al., 2012). This has also been confirmed by meta-analyses, reporting effect sizes between 0.58 and 1.31 for theta power and between 0.62 and 3.08 for TBR (Arns, Conners, & Kraemer, 2013; Boutros, Fraenkel, & Feingold, 2005; Snyder & Hall, 2006). However, a reducing discrepancy in TBR between youngsters with and without ADHD was found across

publication years of studies (Arns et al., 2013). This corresponds with recent studies that could not invariably replicate theta or TBR discrepancies between ADHD and control groups, neither in children, nor in adults (Loo et al., 2009; Ogrim, Kropotov, & Hestad, 2012; van Dongen-Boomsma et al., 2010). Further, in a recent study, theta activity was observed to be enhanced in 60% and reduced in 40% of children with ADHD, highlighting the heterogeneity of spectral EEG in ADHD (Clarke et al., 2011a). Findings regarding beta activity appear even more mixed, with some studies reporting reduced beta power (Lazzaro et al., 1998; Loo et al., 2009) and others documenting no deviances (Bresnahan, Anderson, & Barry, 1999; Clarke, Barry, McCarthy, & Selikowitz, 2001b) or even a beta excess (Chabot & Serfontein, 1996; Clarke, Barry, McCarthy, & Selikowitz, 2001a) in ADHD.

Regarding the differentiation in EEG activity between ADHD predominantly inattentive type (ADHD-I) and ADHD combined type (ADHD-C), disparate findings have been reported. While in some studies individuals with ADHD-I have been documented to demonstrate an in-between pattern of abnormalities between ADHD-C and control subjects (Clarke, Barry, McCarthy, & Selikowitz, 1998; Clarke et al., 2001b; Dupuy, Barry, McCarthy, & Selikowitz, 2011), in others no differences between subtypes (Hermens et al., 2004; Loo et al., 2010; Monastra, Lubar, & Linden, 2001) or greater deviances in ADHD-I compared to ADHD-C (Loo et al., 2010) have been described.

Although theta and TBR are frequently reported to be aberrant in ADHD, their functional significance is not fully understood (Loo & Makeig, 2012). Traditionally, deviating resting state EEG in ADHD (e.g., theta and TBR) has been hypothesized as reflecting hypoarousal in the central nervous system (e.g., Mann, Lubar, Zimmerman, Miller, & Muenchen, 1992; Monastra et al., 1999). However, this account has been challenged since recent studies failed to find an association between a well established measure of arousal (i.e., skin conductance level) and theta or TBR (Barry, Clarke, Johnstone, McCarthy, & Selikowitz, 2009; Clarke et al., 2013). Other researchers have

suggested that the deviances may indicate a maturational delay (e.g., Lazzaro et al., 1998) or developmental deviation (e.g., Hermens et al., 2004) in ADHD as with age EEG power is found to decrease for slow frequencies (e.g., theta) and to increase for faster frequency ranges (e.g., beta) (see Barriga-Paulino, Flores, & Gomez, 2011).

Still, research into the developmental course of EEG in ADHD is scarce. Some evidence has been found for a slower maturation of absolute beta (Satterfield, Schell, Backs, & Hidaka, 1984) and theta (Satterfield et al., 1984; Clarke et al., 2001b) activity in children with ADHD compared to typically developing children. Comparing children with adolescents, a tendency of a smaller decrease in absolute theta power in ADHD relative to a control group has also been reported while no developmental differences were detected when those age groups as a whole were compared with adults (Liechti et al., 2013). Furthermore, along with maturation of EEG in the expected direction, a study documented absolute as well as relative theta activity and TBR to be continuously elevated in ADHD throughout the lifespan, while the amount of reduced relative beta activity in ADHD compared to typically developing individuals decreased with age (Bresnahan et al., 1999). Additionally, a recent longitudinal study revealed that different abnormalities in EEG in childhood preceded persistence and remission of ADHD in adulthood (Clarke et al., 2011b).

Corresponding to the frequently found abnormalities in TBR and theta power across a number of resting EEG studies, the potential of these EEG parameters as diagnostic markers has been proposed, yet remains equivocal. Across studies, sensitivity numbers of TBR in discriminating individuals with and without ADHD vary between 43.8% and 90%, while specificity percentages between 36.7% and 94% are reported (Liechti et al., 2013; Monastra et al., 2001; Snyder et al., 2008). The most recent studies documented an insufficient overall accuracy between 40.3% and 58% for TBR and between 46.8% and 63% for theta power in distinguishing children with ADHD from a control group (Liechti et al., 2013; Ogrim et al., 2012). Besides, increased theta appears

to be a nonspecific phenomenon common to other disorders such as epilepsy, bipolar disorder, substance abuse, dementia, alcoholism and schizophrenia (Coutin-Churchman et al., 2003).

In the current study, eyes closed resting EEG was analyzed in children and adults with and without ADHD to gain further insights into the developmental course and diagnostic potential of resting EEG in ADHD (subtypes) throughout the lifespan. As most of the normative databases used in clinical practice to compare EEG activity are based on eyes closed resting EEG data, it is important to investigate eyes closed resting conditions in clinical populations (Clarke et al., 2008). If theta power and TBR are significant markers for ADHD across the lifespan, these EEG parameters were expected to be elevated in children as well as in adults with ADHD and consequently successful in distinguishing individuals with ADHD from typically developing individuals. Previous research addressing differences between inattentive and combined subtype or divergence in maturational changes between the ADHD and control group is scarce and revealed inconsistent results, which makes it difficult to formulate specific hypotheses.

METHOD

Participants

Sixty-six children (30 without ADHD, 36 with ADHD) aged 7 to 14 years and 51 adults (25 without ADHD, 26 with ADHD) aged 18 to 55 years participated in the study (see Table 1). Participants were recruited through staff members, schools, advertisements, neurologists and self support groups for ADHD. Individuals with ADHD were previously diagnosed in a clinical setting according to DSM-IV criteria. Diagnosis was ascertained by a semi-structured clinical interview (behavioural module of Diagnostic Interview Schedule for Children IV for children, Schaffer, Fisher, Lusac,

Dulcan, & Schwab-Stone, 2000; Diagnostisch Interview Voor ADHD bij Volwassenen 2.0 for adults, Kooij & Francken, 2010). The Disruptive Behavior Disorder Rating Scale (DBD, Pelham, Gnagy, Greenslade, & Milich, 1992) was administered to furthermore evaluate ADHD symptoms in children. Presence of childhood ADHD in adults was retrospectively assessed with the Wender Utah Rating Scale (Ward, Wender, & Reimherr, 1993), whereas ADHD manifestation through the lifespan was evaluated with the ADHD Rating Scale-IV (ADHD-RS, DuPaul, Power, Anastopoulos, & Reid, 1998). Following published diagnostic guidelines (Kooij et al., 2010), adults were required to exhibit at least 4 symptoms in the inattentive and/or the hyperactive/impulsive domain to meet criteria for ADHD during adulthood. Individuals with ADHD using stimulants were asked to refrain from medication 48 hours before participation in the experiment. Exclusion criteria for all participants were history of brain related illness, neurological disorder, suspicion of autism spectrum disorder and estimated IQ below 80. Intelligence functioning was evaluated by an abbreviated Wechsler Intelligence Scale for Children-III (Wechsler, 1991; Grégoire, 2000) or Wechsler Adult Intelligence Scale-III (Wechsler, 1997; Ryan & Ward, 1999). Individuals reaching clinical scores on ADHD rating scales and on the Child Behavior Checklist (for children) or Adult Self Report (for adults) (Achenbach & Rescorla, 2001, 2003) were excluded from the control groups.

Table 1. Sample characteristics

	CONTROL (*n* = 55)	ADHD (*n* = 62)
Children	*n* = 30	*n* = 36
Age in years	*M* 10.46 (*SD* 1.75)	*M* 10.11 (*SD* 1.82)
Estimated FSIQ (WISC)	*M* 108.10 (*SD* 11.55)	*M* 104.89 (*SD* 12.95)
Male/female	15/15	26/10
ADHD C/I	-	14/22
Stimulants (Yes/No)	-	20/16
Adults	*n* = 25	*n* = 26
Age in years	*M* 35.32 (*SD* 11.12)	*M* 33.76 (*SD* 10.17)
Estimated FSIQ (WAIS)	*M* 111.96 (*SD* 10.87)	*M* 109.96 (*SD* 12.16)
Male/female	14/11	12/14
ADHD C/I	-	15/11
Stimulants (Yes/No)	-	12/14

Note. FSIQ: Full Scale Intelligence Quotient, WISC: Wechsler Intelligence Scale for Children, *M*: mean, *SD*: standard deviation, ADHD: Attention Deficit Hyperactivity Disorder, C: Combined subtype, I: Inattentive subtype, WAIS: Wechsler Adult Intelligence Scale

Procedure

The research protocol was approved by the local ethics committee and all participants or their parents signed an informed consent. The protocol involved recordings of resting EEG and execution of neuropsychological tasks. The present study focussed on three minutes eyes closed resting EEG.

EEG data were obtained with an electrode cap employing 128 active Ag/AgCl electrodes (EasyCap Active, EasyCap GmbH) placed according to the 10-5 International System (Oostenveld & Praamstra, 2001). Signals were amplified with an open pass-band from DC to 100 Hz with a QuickAmp amplifier (Brain Products, Gilching, Germany) and digitized using Brain Vision Recorder software (version 1.10) with a sample rate of 500 Hz and an average reference derivation. The ground electrode was mounted within the

cap at Fpz. Electro-oculogram was recorded with electrodes enclosed in the cap near the eyes and for adults, an additional electrode was placed below the right eye.

Analyses of EEG data were performed using Brain Vision Analyzer software (version 2.0.1). EEG data were filtered with a high pass filter of 0.5 Hz, a low pass filter of 50 Hz and a notch filter of 50 Hz. Data were segmented in 2 s epochs with 1 s overlap. Eye movement correction was conducted according to the Gratton & Coles algorithm (Gratton, Coles, & Donchin, 1983). Segments were rejected from further analyses if amplitudes exceeded ±100 μV for children and if absolute difference in amplitudes exceeded 120 μV for adults. Subsequently, spectral power was calculated using Fast Fourier Transform and the transformed data were averaged. For replication purposes (e.g., Liechti et al., 2013; Ogrim et al., 2012), absolute and relative power estimates were derived for theta (3.5-7.5 Hz) and beta (12.5-25 Hz) frequencies at frontal (Fz), central (Cz) and parietal (Pz) midline. Relative power was computed by dividing the average power in a frequency band by the total average power in the 1.5-25 Hz spectrum, multiplied by 100 (see also Dupuy et al., 2011). TBR was calculated by dividing power in the theta band by power in the beta band. A natural logarithmic transform was used to approach normal spreading of the data.

Statistical analyses

EEG activity across the lifespan in the ADHD and control group was compared by separate analyses of variance with repeated measures for absolute as well as relative theta and beta power and for TBR. Midline electrode position (Fz, Cz, Pz) was the within-subject factor and clinical group (ADHD, non-ADHD) and age group (child, adult) were between-subject factors. Effect sizes were determined by partial eta squared (η^2_p) and, according to guidelines (Cohen, 1988), are interpreted as small (< .06), medium (.06 - .14), or large (> .14).

Receiver operation characteristic (ROC) curves were computed for determining the accuracy of logistic regression models of absolute as well as relative theta and beta power and TBR at the vertex in predicting clinical and age group membership. Cz was examined to warrant comparability with other publications, since most studies documenting on diagnostic validity of EEG parameters in ADHD have investigated EEG activity at the vertex (Liechti et al., 2013; Monastra et al., 1999, 2001; Ogrim et al., 2012; Snyder et al., 2008). First, binary logistic regression was performed to predict probabilities for each EEG parameter separately. Then, ROC curves were computed to determine the efficacy of the predicted probabilities in the respective binary outcomes of interest (i.e., age group and clinical diagnosis group). Accuracy is indicated by the area under the ROC curve, in which the reference line represents the null hypothesis (Ogrim et al., 2012).

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) volume 20.

RESULTS

EEG

Concerning clinical group effects, none of the EEG measures reached significance (see Table 2). Incorporation of sex as a covariate did not change the results significantly, neither did repeating analyses including only individuals expressing at least 6 symptoms in one or both domains of symptomatology in the adult ADHD group (i.e., 22 adults). Also, effect sizes were fairly similar in these additional analyses.

Regarding age group effects, children demonstrated higher absolute theta ($F(1, 111) = 281.51$, $p < .001$) and beta ($F(1, 111) = 19.85$, $p < .001$) power than adults. Regarding relative power, higher theta ($F(1, 111) = 97.73$, $p < .001$) as well as lower beta ($F(1, 111)$

= 62.67, $p < .001$) activity were found in children compared to adults. Furthermore, a higher TBR ($F(1, 111) = 169.44$, $p < .001$) was observed in childhood relative to adulthood. Considering the scope of the present study, divergence between children and adults associated with electrode positions will not be elaborated on.

Table 2. Repeated measures analyses of variance per EEG parameter: controls versus ADHD

Clinical group				Age group		Electrode
	x age group	x electrode	x age group x electrode		x electrode	
	F(1, 226)	*F*(1, 113)	*F*(2, 226)	*F*(2, 226)	*F*(1, 113)	*F*(2, 226)	*F*(2, 226)
	(η^2_p)	(η^2_p)	(η^2_p)	(η^2_p)	(η^2_p)	(η^2_p)	(η^2_p)
aθ							
	0.24	0.80	0.06	0.48	280.35***	0.44	0.03
	(.00)	(.01)	(.00)	(.00)	(.71)	(.00)	(.00)
rθ							
	0.01	0.02	0.32	0.22	101.91***	0.33	96.56***
	(.00)	(.00)	(.00)	(.00)	(.47)	(.00)	(.46)
aβ							
	0.33	0.05	0.09	0.92	19.22***	1.52	4.21*
	(.00)	(.00)	(.00)	(.01)	(.15)	(.01)	(.04)
rβ							
	1.71	0.57	0.13	1.25	65.16***	11.86***	19.75***
	(.02)	(.01)	(.00)	(.01)	(.37)	(.10)	(.15)
TBR							
	1.38	0.51	0.22	0.37	173.10***	6.31**	10.90***
	(.01)	(.00)	(.00)	(.00)	(.61)	(.05)	(.09)

Note. aθ: absolute theta power, rθ: relative theta power, aβ: absolute beta power, rβ: relative beta power, TBR: theta/beta ratio, * $p < .05$, ** $p < .01$, *** $p < .001$

Since our results did not indicate differences between individuals with and without ADHD and literature points out that EEG deviances may differ across ADHD subtypes (e.g., Clarke et al., 1998), additional analyses of variance with repeated measures were performed where the within subject factor clinical group was subdivided in non-ADHD (i.e., 55 individuals), ADHD-C (i.e., 29 individuals) and ADHD-I (i.e., 33 individuals).

Results regarding absolute theta and beta power as well as relative theta power did not change significantly, however main group effects appeared for relative beta power ($F(2, 111) = 3.81$, $p = .03$) and TBR ($F(2, 111) = 6.06$, $p < .01$). Bonferroni post hoc analyses indicated reduced relative beta power and enhanced TBR in individuals with ADHD-I compared to the other groups (see Figure 1 and Table 3).

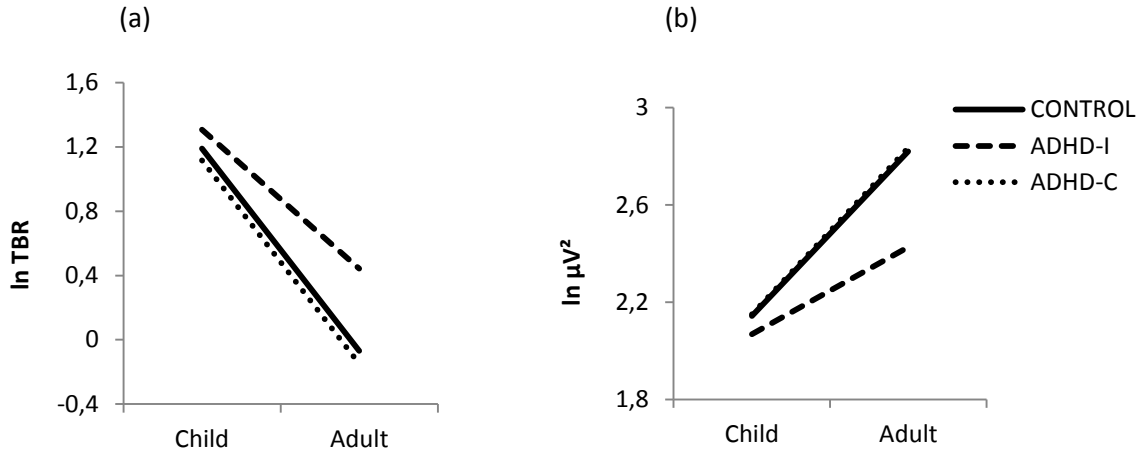

Figure 1. Mean (a) TBR and (b) relative beta power at Cz for children and adults without ADHD, with ADHD-I and with ADHD-C.

Table 3. Repeated measures analyses of variance per EEG parameter with clinical groups non-ADHD versus ADHD-I versus ADHD-C

	Clinical group				Age group		Electrode
		x age group	x electrode	x age group x electrode		x electrode	
	F(1, 222)	*F*(1, 111)	*F*(2, 222)	*F*(2, 222)	*F*(1, 111)	*F*(2, 222)	*F*(2, 222)
	(η^2_p)	(η^2_p)	(η^2_p)	(η^2_p)	(η^2_p)	(η^2_p)	(η^2_p)
rβ							
	3.81*	1.74	0.11	0.96	52.56***	8.76***	17.82***
	(.06)	(.03)	(.00)	(.02)	(.32)	(.07)	(.14)
TBR							
	6.06**	1.98	0.39	0.43	151.42***	4.90**	9.68***
	(.10)	(.03)	(.01)	(.01)	(.58)	(.04)	(.08)

Note. rβ: relative beta power, TBR: theta/beta ratio, *$p < .05$, **$p < .01$, ***$p < .001$

Classification analysis

ROC analyses indicated that EEG parameters were unsuccessful in distinguishing individuals with ADHD from typically developing individuals (accuracy rates varied between 49.2% and 54.8%). Additional analyses restricted to discrimination of individuals with ADHD-I did not substantially increase the accuracy (e.g., highest accuracy rate was 64%). However, children and adults could be successfully discriminated based on absolute as well as relative theta power, relative beta power and TBR (accuracy rates varied between 89.8% and 96.5%). Absolute beta power was less effective in discriminating children from adults (see Figure 2 and Table 4).

(a) (b)

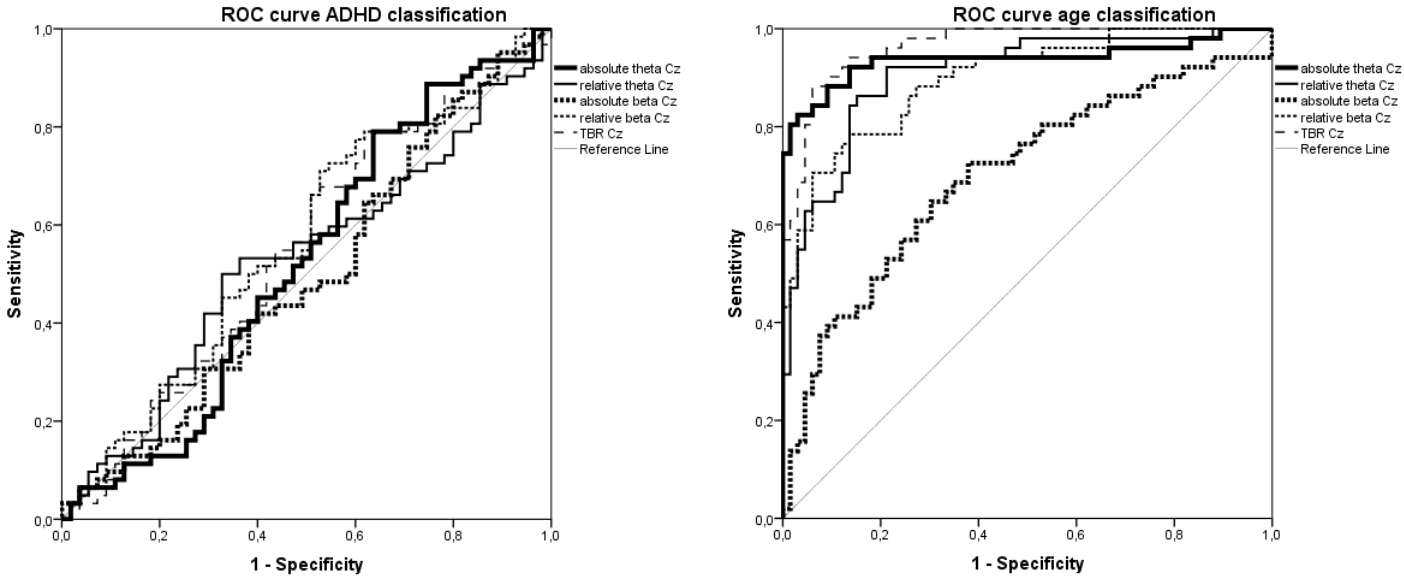

Figure 2. ROC curves expressing accuracy of EEG parameters in (a) ADHD and (b) age classification.

Table 4. ADHD and age classification based on EEG parameters

	EEG parameter	AUC	*p*
ADHD (C+I) classification			
	aθ	0.52	0.71
	rθ	0.53	0.62
	aβ	0.50	0.88
	rβ	0.56	0.25
	TBR	0.55	0.37
ADHD-I classification			
	aθ	0.57	0.30
	rθ	0.60	0.14
	aβ	0.53	0.65
	rβ	0.64	0.03
	TBR	0.63	0.04
Age classification			
	aθ	0.94	0.00
	rθ	0.91	0.00
	aβ	0.70	0.00
	rβ	0.90	0.00
	TBR	0.97	0.00

Note. AUC: area under the curve, C: Combined subtype, I: Inattentive subtype

DISCUSSION

In the current study, no EEG differences were found between the total ADHD group (i.e., comprising both ADHD-I and ADHD-C) and the healthy control group. Also, no divergence in the developmental course of EEG activity was found between those groups. However, further analyses detected an elevated TBR and reduced relative beta power across the lifespan in ADHD-I compared to ADHD-C and controls.

Although our findings of comparable EEG profiles and developmental pathways of individuals with ADHD-C and typically developing controls disaccord with previous

reports on theta and TBR deviances in ADHD (for a review, see Barry et al., 2003), they correspond with a few recent studies that also failed to replicate theta and TBR abnormalities in ADHD relative to typically developing individuals (e.g., van Dongen-Boomsma et al., 2010; Liechti et al., 2013). Furthermore, our results are in line with findings of a smaller difference in TBR between ADHD and normal controls in more recent publications compared to earlier studies (Arns et al., 2013). It is plausible that differences in inclusion and exclusion criteria for control subjects as well as ADHD patients have contributed to different findings across studies (Arns et al., 2013; Liechti et al., 2013). As for the current study, it seems unlikely that the predominance of boys in the child ADHD group contributed to the failure of finding EEG abnormalities in children with ADHD, since supplementary analyses controlling for sex did not change the results significantly. Besides, given that some studies documented more deviances in ADHD boys compared to girls (e.g., Clarke et al., 2001b), this would rather have resulted in detecting instead of overlooking abnormalities in our sample. Lowering the cut-off of symptomatology for incorporating adults with ADHD in our study did also not impede finding EEG differences between individuals with ADHD and typically developing individuals since additional analyses using a more restrictive symptom threshold for including adults did not affect the significance of findings. Moreover, this cannot explain the absence of differences between children with and without ADHD. The current ADHD sample comprised both individuals diagnosed with the ADHD combined as well as the inattentive subtype. This differs from studies that incorporated only individuals with ADHD combined subtype (e.g., Liechti et al., 2013; van Dongen-Boomsma et al., 2010) but accords with others that included individuals with different ADHD subtypes (e.g., Loo et al., 2010; Ogrim et al., 2012). Only a few studies directly compared the combined and

inattentive subtype and presented mixed results, making comparability to existing literature difficult. Furthermore, exclusion and inclusion criteria regarding comorbid disorders in individuals with ADHD are different across studies and the influence of comorbidity on resting EEG findings in ADHD has not been investigated systematically. Also in the current study, comorbid problems were present in individuals with ADHD as indicated by elevated symptoms of anxiety/depression, learning disorders and disruptive behaviour measured through interviews and questionnaires. Future studies with larger sample sizes are needed to evaluate the impact of comorbidity on resting EEG findings in ADHD. These factors, as well as the relatively high intelligence profile of our ADHD sample compared to other studies, may confound the comparability of our study to others and therefore impede generalisability of the results.

Few EEG studies have addressed the comparison of ADHD-I and ADHD-C, and yielded disparate findings. In some studies, both ADHD subtypes similarly deviated from a control group, while in others, more pronounced quantitative EEG differences in one subtype relative to the other and/or the control group were documented (Clarke et al., 1998, 2001b; Dupuy et al., 2011; Hermens et al., 2004; Loo et al., 2010). In this study, the observed larger EEG deviances in ADHD-I were not accounted for by a greater severity of inattention problems in the ADHD-I group compared to the ADHD-C group, as inattention scores as derived from the questionnaires did not differ between ADHD-I and ADHD-C. Also, ADHD subtypes did not differ on severity of comorbid problems as screened by the subscales of Achenbach questionnaires. Our findings may suggest that distinct types of inattention characterize differences between ADHD-I and ADHD-C, involving different neural circuits, rather than variations in symptom severity (Diamond, 2005; Milich, Balentine, & Lynam, 2001). However, this statement cannot unequivocally

be confirmed by our data. Moreover, this interpretation discords with a recent meta-analysis of 546 studies, that found minimal support for defining ADHD-I and ADHD-C as distinct disorders (Willcutt et al., 2012). In view of the literature that defined EEG based subgroups in ADHD through cluster analyses (Clarke et al., 2011a), our findings may be better explained as emphasizing heterogeneity of EEG in ADHD, confirming deviances in a subgroup of patients rather than in the whole ADHD group.

Since EEG deviances were found to persist throughout the lifespan, it seems questionable that a maturational delay may account for EEG discrepancies in a subgroup of individuals with ADHD. A developmental deviance may be a better interpretation of these results. However, findings should be seen as tentative since direct individual measurements of developmental changes are not provided in this cross sectional study. Ideally, longitudinal designs are applied in gaining more insights in the nature of the developmental course of EEG deviances in ADHD(-I).

Given the lack of consistent EEG abnormalities in the ADHD group, the accuracy rates reflecting failure in discriminating this group from the control group based on these parameters was not surprising. Our overall accuracy rates below 57% align with recent documents, that also demonstrated inadequacy of EEG based classification (Liechti et al., 2013; Ogrim et al., 2012) but contrast with earlier findings of accuracy rates up to 90% (Monastra et al., 2001; Snyder et al., 2008). Alternatively, accuracy in distinguishing children from adults attained 96.5% despite using parameters selected for deviances in ADHD. Since our findings regarding maturation of EEG activity are consistent with literature (e.g., Barriga-Paulino et al., 2011), we believe our data would have allowed reliable detection of a maturational lag, as has been suggested for ADHD.

In sum, our EEG findings confirm the view that ADHD is a heterogeneous disorder, which is also established in multiple pathway models of ADHD (e.g., Sonuga-Barke, Bitsakou, & Thompson, 2010). Our results suggest that it is unlikely that ADHD is characterized by generalised EEG abnormalities and that the use of conventional EEG practices as a diagnostic adds-on in ADHD has to be regarded as insufficient. However, since reduced relative beta power and elevated TBR were found in a subgroup of patients, it seems plausible that EEG measures may be of interest in guiding prognostic practices. That is, they may possibly be applied to distinguish subgroups that respond differently to various treatments. This has already been illustrated in research investigating the relationship between EEG parameters and treatment response to stimulant medication (Arns, Gunkelman, Breteler, & Spronk, 2008) and neurofeedback treatment (Arns, Drinkenburg, & Kenemans, 2012).

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CHAPTER 3

EEG ACTIVITY BEFORE AND AFTER COGNITIVE EFFORT IN CHILDREN WITH ADHD[1]

ABSTRACT

Objective: This study investigated whether children with attention-deficit/hyperactivity disorder (ADHD) show a deviant electroencephalographic (EEG) pattern and whether this is stable across resting state conditions before and after cognitive effort. **Methods**: Three minutes eyes closed resting EEG before and after cognitive effort were compared between 21 children with ADHD and 22 typically developing children. **Results**: Groups did not differ in any of the EEG measures. However, the progressive topographic expansion in alpha power from anterior to posterior sites was lower in children with ADHD across conditions. Posterior absolute delta, theta and beta power, central absolute beta power, and relative theta power attenuated, while central relative delta power increased after task execution in both groups. No group differences were detected in EEG changes following cognitive effort. **Conclusions**: Despite the lack of finding group differences in theta or theta/beta ratio, topographic organization of alpha power was detected to differ between groups, independent of condition. Although EEG activity changed after cognitive effort in both groups, the findings did not indicate altered changes after task execution in ADHD.

[1] Based on Buyck, I., & Wiersema, J.R. (2014). *Electroencephalographic activity before and after cognitive effort in children with attention deficit hyperactivity disorder.* Manuscript submitted for publication.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neurobehavioural disorder with a childhood onset that is characterized by developmentally incompatible symptoms of inattention and/or hyperactivity/impulsivity, leading to impairment in multiple life domains (American Psychiatric Association, 2013). The worldwide prevalence rates of ADHD are estimated between 5 and 7% (Willcutt, 2012). In the past decades, electroencephalographic (EEG) measures, particularly during resting conditions, have been frequently used to determine whether neurophysiological abnormalities may be associated with ADHD.

Resting EEG studies in ADHD have mainly focussed on children, in which differences in EEG patterns have been observed compared to typically developing children. That is, children with ADHD commonly show increased absolute or relative theta activity and/or an elevated theta/beta ratio (TBR) (for a review, see Barry, Clarke, & Johnstone, 2003; Buyck & Wiersema, 2014; Clarke, Barry, McCarthy, Selikowitz, & Johnstone, 2007; Clarke et al., 2011; Dupuy, Clarke, Barry, McCarthy, & Selikowitz, 2011; González-Castro, Rodríguez, López, Cueli, & Álvarez, 2013; Lansbergen, Arns, van Dongen-Boomsma, Spronk, & Buitelaar, 2011; Loo et al., 2010; Shi et al., 2012). Although not systematically addressed in studies, increased absolute or relative delta activity has been observed as well in children with ADHD (Clarke, Barry, McCarthy, & Selikowitz, 1998; Clarke, Barry, McCarthy, & Selikowitz, 2001a; Clarke et al., 2007). Yet, lately the robustness of EEG slowing characterizing the total ADHD group has been challenged, since several recent studies could not invariably replicate the typically increased theta power or TBR in children with ADHD relative to typically developing children found in earlier studies (Coolidge, Starkey, & Cahill, 2007; Liechti et al., 2013; Loo et al., 2013; Nazari, Wallois, Aarabi, & Berquin, 2011; Ogrim, Kropotov, & Hestad, 2012; Swartwood, Swartwood, Lubar, & Timmermann, 2003). This was also confirmed by a recent meta-analysis that revealed a reducing discrepancy in TBR between

youngsters with and without ADHD across publication years of studies in the last decade (Arns, Conners, & Kraemer, 2013). Additionally, recent studies denoted that enhanced theta or TBR was only apparent in about 20 to 60% of children (Arns, Drinkenburg, & Kenemans, 2012; Clarke et al., 2011; Ogrim et al., 2012), and that theta can even be reduced in a part of children with ADHD (Clarke et al., 2011). Concerning activity in the faster frequency bands, findings are even more ambiguous. Regarding alpha activity, most studies refer to a reduced amount of absolute or relative alpha (Clarke et al., 1998, 2001a; Clarke, Barry, McCarthy, & Selikowitz, 2002a; Clarke et al., 2003; Barry, Clarke, Johnstone, McCarthy, & Selikowitz, 2009) but increased activity in the alpha band has also been reported in a subgroup of ADHD (Chabot & Serfontein, 1996; Clarke et al., 2011). Even so, some studies failed to detect deviance in alpha power in ADHD (Loo et al., 2010; Shi et al., 2012). Likewise, reduced absolute or relative beta activity has often been detected in children with ADHD (Clarke et al., 1998, 2002a, 2003; Shi et al., 2012) but in a small group, excess beta activity has been observed instead (Chabot & Serfontein, 1996; Clarke et al., 1998; Clarke, Barry, McCarthy, & Selikowitz, 2001b), while in other studies no significant group distinction in beta power was found (Liechti et al., 2013; Loo et al., 2010).

Interestingly, in ADHD it is well-established that behavioural symptoms (Antrop, Buysse, Roeyers, & Van Oost, 2005; Zentall & Zental, 1983), performance (Luman, Oosterlaan, & Sergeant, 2005; Power, 1992; Sonuga-Barke, Williams, Hall, & Saxton, 1996; Toplak & Tannock, 2005; Wiersema, van der Meere, Antrop & Roeyers, 2006a; Wiersema, van der Meere, Roeyers, Van Coster, & Baeyens, 2006b) as well as physiological parameters (Benikos & Johnstone, 2009; Börger & van der Meere, 2000; Imeraj et al., 2011, 2012; Kooistra et al., 2010; Wiersema et al., 2006a,b) fluctuate over time and in response to changing environmental contexts. In this respect, there has been mounting evidence that contextual factors play a crucial role in determining to which extent performance is deficient in ADHD (Sonuga-Barke, Wiersema, van der

Meere, & Roeyers, 2010). For instance, it has repeatedly been found that performance of children with ADHD heavily depends on energetic state related factors, with impairments especially apparent in conditions that induce suboptimal arousal/activation state, such as slow presentation rate of stimuli (for a meta-analysis, see Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012; Scheres, Oosterlaan, & Sergeant, 2001; Wiersema et al., 2006a,b). Based on these and other findings, the important role of contextual factors in the explanation of the deficits associated with ADHD has been acknowledged by several theoretical frameworks. That is, the state regulation deficits model (Sergeant, 2005; van der Meere, 2005) and the delay aversion model (Sonuga-Barke, Taylor, Sembi, & Smith, 1992) emphasize respectively dynamic underlying failures of energetic or motivational state factors in ADHD (Sonuga-Barke et al., 2010).

As abnormalities in ADHD have been found to be dependent on contextual and state factors, the question can be raised whether the apparent discrepant findings between resting EEG studies -among others (i.e., sample characteristics, EEG recording and quantification procedures, …)- can partially be explained by differences in state-related factors between studies. Although research has found support for intra-individual stability of EEG in typically developing children over time (e.g., Fein, Galin, Yingling, Johnstone, & Nelson, 1984; Gasser, Bacher, & Steinberg, 1985), contextual and state influences are also well known to affect EEG (e.g., Antonenko, Paas, Grabner, & van Gog, 2010; Barry, Clarke, Johnstone, Magee, & Rushby, 2007; Kim, Kim, Oh, & Kim, 2013; Oken, Salinsky, & Elsas, 2006). An illustration of a widely recognized state factor that influences EEG activity refers to the opening of the eyes (e.g., Barry et al., 2007). Regarding this, most studies in ADHD have addressed EEG in either an eyes closed or an eyes opened resting condition, with only a few evaluating both resting conditions (Fonseca, Tedrus, Bianchini, & Silva, 2013; Lansbergen et al., 2011; Liechti et al., 2013; Loo et al., 2010, 2013). Interestingly, some of these latter studies have detected that conditions with closed eyes generated greater discrepancies between groups in absolute

theta power (Liechti et al., 2013) and TBR (Lansbergen et al., 2011) than resting conditions with open eyes. Further, a greater theta power increase to eye closing (Liechti et al., 2013) and a reduced alpha suppression to eye opening (Buyck & Wiersema, submitted; Fonseca et al., 2013) have been found in children with ADHD. These findings suggest that contextual and state factors are important to take into account when evaluating EEG deviances in ADHD. Keeping up with this, less is known about the impact of timing of EEG measurement during experiments in EEG divergence between groups, since so far research focussed on either starting (e.g., Snyder et al., 2008) or ending (e.g., Dupuy et al., 2011) laboratory visits with EEG registration without including both conditions. Studies suggest that both conditions are able to unfold EEG deviances in ADHD, but the lack of literature addressing both EEG registration before and after cognitive effort in one and the same study impedes drawing conclusions on possible divergence and transition, and thus context dependent changes, between measurements. To our knowledge only one study evaluated EEG before and after cognitive effort in ADHD, be it in adults (Koehler et al., 2009). In this study, beta power increased after task execution in controls, but not in adults with ADHD (Koehler et al., 2009). Yet, although research addressing the subsequent influences of cognitive effort on resting conditions in a normal population is scarce as well and also limited to adults, several studies point to changes in resting EEG after task execution (Smit, Eling, & Coenen, 2004; Smit, Eling, Hopman, & Coenen, 2005; Tanaka et al., 2012), revealing the impact of this contextual factor on EEG activity. In typically developing adults, eyes closed absolute (Smit et al., 2004) and relative theta (Smit et al., 2005) as well as absolute beta power (Smit et al., 2004) have been documented to increase following demanding cognitive tasks. In a more recent study, it was established that EEG activity was not found to be modulated after completing an easy 0-back task, whereas decreased posterior alpha and beta power and increased theta activity emerged after a more demanding 2-back task (Tanaka et al., 2012). Although it is clear that task

execution affects subsequent resting EEG activity, the inconsistency in existent findings suggest that also task-related features contribute to the nature of EEG changes after cognitive effort.

Taken together the above-mentioned notions, the question rises whether context or state dependent fluctuations may not only be reflected in behaviour, performance and certain physiological indices, but also in quantitative EEG in ADHD. As outlined above, some support can be found for this hypothesis through studies evaluating both eyes closed and eyes open resting conditions. Given the paucity of literature, the present study aims to expand insights on context-related EEG divergence in ADHD by investigating whether possible EEG deviances in ADHD are stable before and after task execution and to what extent intervening task execution interferes with characterizing resting EEG deviances in ADHD. It is imperative to shed light on those dynamic changes in EEG in ADHD, since nowadays an increasing number of clinicians use EEG for assessment and treatment guidance in which quantitative EEG of individuals with ADHD is compared to normative databases. If there are indications that dynamic factors affect EEG abnormalities in ADHD, this may have important consequences in dealing with these databases for clinical purposes, where insufficient knowledge may result in ineffective practices and even cause iatrogenic harm (Hammond, 2010). As most of these databases are based on eyes closed resting EEG data, it is important to investigate eyes closed resting conditions in clinical populations (Clarke et al., 2008). Therefore, in the present study resting EEG activity is evaluated in children with and without ADHD in eyes closed resting conditions before and after task execution.

If theta power and TBR are solid markers for ADHD that may be regarded as a stable characteristic, then these EEG parameters are expected to be enhanced in children with ADHD in both resting conditions. If however an interaction is detected between group divergence and timing of EEG registration, this would indicate that state-related factors may be associated with EEG abnormalities in ADHD.

METHOD

Participants

Twenty-one children diagnosed with ADHD and 22 typically developing children aged 7 to 14 years participated in the study (Table 1). Groups were matched for sex and age ($F(1, 41) = 0.00$, $p = .99$) and did not differ in IQ ($F(1, 41) = 2.83$, $p = .10$). Participants were recruited through advertisements, schools, staff members and, specifically for ADHD, child neurologists. Children with ADHD were previously diagnosed in a clinical setting according to DSM-IV criteria. The diagnosis was confirmed using the parent version of the behavioural module of the Diagnostic Interview Schedule for Children IV for children (DISC-IV) (Schaffer, Fisher, Lusac, Dulcan, & Schwab-Stone, 2000). Furthermore, the Disruptive Behavior Disorder (DBD) Rating Scale (Pelham, Gnagy, Greenslade, & Milich, 1992; Dutch translation: Oosterlaan, Scheres, Antrop, Roeyers, & Sergeant, 2000) was used to evaluate ADHD symptoms, while the Child Behavior Checklist (Achenbach & Rescorla, 2001) was administered to screen for psychiatric disorders. IQ was evaluated by an abbreviated Wechsler Intelligence Scale for Children-III, including the subtests Vocabulary, Similarities, Block design and Picture Arrangement (Wechsler, 1991; Grégoire, 2000). Exclusion criteria for all participants were history of brain related illness, neurological disorder, learning disorder and estimated IQ below 80. Children reaching clinical scores on the DBD Rating Scale and on the Child Behavior Checklist were excluded from the group of typically developing children. To control for medication effects, children with ADHD using stimulants respected a wash-out period of 48 hours before participating in the experiment.

The participants in the present study largely overlap with the children that have been incorporated in the study of Buyck and Wiersema (2014). Also, the current data reported in the eyes closed condition before task execution, partially overlap with data from the aforementioned study.

Table 1. Sample characteristics

	CONTROL (*n* = 22)	ADHD (*n* = 21)
Age in years	*M* 10.21 (*SD* 1.50)	*M* 10.20 (*SD* 1.73)
Estimated FSIQ	*M* 109.09 (*SD* 10.93)	*M* 103.10 (*SD* 12.43)
Boys/girls	14/8	13/8
ADHD I/H/C	-	9/1/11
Stimulants (Yes/No)	-	11/10

Note. FSIQ: Full Scale Intelligence Quotient, *M*: mean, *SD*: standard deviation ADHD: Attention Deficit Hyperactivity Disorder, I: Inattentive subtype, H: Hyperactive/Impulsive subtype, C: Combined subtype

Procedure

The research protocol was approved by the ethic committee of the Faculty of Psychology and Educational Sciences at Ghent University and all parents signed an informed consent before the children participated in the experiment. All questionnaires were filled in at home. Administration of the DISC-IV and evaluation of intelligence functioning took place in another session than electrophysiological recordings. However, for some children with ADHD, intelligence functioning was estimated right after EEG registration. Regarding EEG recording, children were asked to sit down in front of a monitor and were then fitted with the electrophysiological equipment. Resting state EEG was recorded in eyes closed and eyes open for three minutes each. Subsequently, instructions were given to perform a slow paced 0-back task, a regular paced 0-back task and a regular paced 1-back task. During the tasks, a red square was displayed for 500 ms in either the upper left, upper right, lower left or lower right of a white cubic that was presented in the middle of a computer screen. In the 0-back task, children were asked to press the left mouse button when the red square was presented at the upper left and the right button when the square was presented at any of the other locations of the cubic. In the 1-back task, participants had to respond by pushing the left button when the stimulus was presented at the same location as the previous

trial and pushing the right button when the red square was displayed at another location. In the slow paced 0-back task, inter stimulus interval was 6000 ms, whereas in the regular paced 0 back and 1 back tasks, inter stimulus interval was 2000 ms. Each task consisted of 8 practice items to assure task comprehension, followed by 96 trials in the slow paced task and 240 trials in the regular paced tasks. Including administration of practice blocks, the total task completion took about forty minutes. At the end of the session, resting state EEG was again recorded for three minutes with closed and open eyes. Resting state EEG recordings (eyes closed and open) were administered in a counterbalanced order, as was implementation of the three tasks. The current study focussed on the eyes closed resting EEG conditions before and after task execution as most of the normative databases used in clinical practice to evaluate EEG are based on eyes closed conditions.

Electrophysiological measures

EEG activity was recorded using a 128 electrode cap with 10 mm Ag/AgCl electrodes (EasyCap Active, EasyCap GmbH) placed according to the 10-5 International System (Oostenveld & Praamstra, 2001). Data were average referenced with the ground electrode mounted within the cap at Fpz. Brain Vision Recorder software (version 1.10, Brain Products, Gilching, Germany) was used to digitize signals with a sample rate of 500 Hz. Signals were amplified with an open pass-band from direct current to 100 Hz with a QuickAmp amplifier (Brain Products, Gilching, Germany). Electro-oculogram was recorded with electrodes enclosed in the cap near the eyes.

EEG data were analysed using Brain Vision Analyzer software (version 2.0.1). Signals were filtered offline with a 0.5 Hz to 50 Hz band-pass and a notch filter of 50 Hz. Data were segmented in 2 s epochs with 1 s overlap. After ocular artefact correction according to the Gratton & Coles algorithm (Gratton, Coles, & Donchin, 1983), segments were rejected from further analyses if amplitudes exceeded ±100 µV. Subsequently,

spectral power was calculated using Fast Fourier Transform, applying a Hanning window of 20%. The average used segments for analyses respectively before and after task execution were 120.2 (*SD* = 30.8) and 118.9 (*SD* = 31.5) for the control group and 107.5 (*SD* = 30.7) and 108.0 (*SD* = 34.0) for the ADHD group. The number of segments did not significantly differ between conditions ($F(1, 41) = 1.32$, $p = .26$) or between groups ($F(1, 41) = 3.68$, $p = .06$). Absolute and relative power estimates were derived from the average for the delta (1.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz) and beta (12.5-25 Hz) frequency. Relative power was computed by dividing the average power in a frequency band by the total average power in the 1.5-25 Hz spectrum, subsequently multiplied by 100 to reach percentages (see also Dupuy et al., 2011). Theta/beta power ratio was calculated by dividing the power of the theta band by the power of the beta band. Nine regions were derived for analyses: left frontal (AF3, F3, F7), midline frontal (Fz, FCz), right frontal (AF4, F4, F8), left central (T7, C3), midline central (Cz), right central (T8, C4), left posterior (P7, P3, O1), midline posterior (Pz, Oz) and right posterior (P8, P4, O2) (see also Barry et al., 2009). A natural logarithmic transform, ln(x), was administered to approach normal spreading of the data.

Statistical analyses

EEG activity before and after task execution in children with and without ADHD was compared by running separate analyses of variance with repeated measures for each absolute and relative EEG measure with time point (before, after task execution), sagittal region (frontal, central, posterior) and lateral region (left, midline, right) as within-subject factors and group (ADHD, control) as between-subject factor.

As gender and age may affect EEG differences (e.g., Clarke et al., 2001a; Dupuy, Barry, Clarke, McCarthy, & Selikowitz, 2013), additional analyses were run with those factors as a covariate. Whenever the assumption of sphericity was violated in analyses,

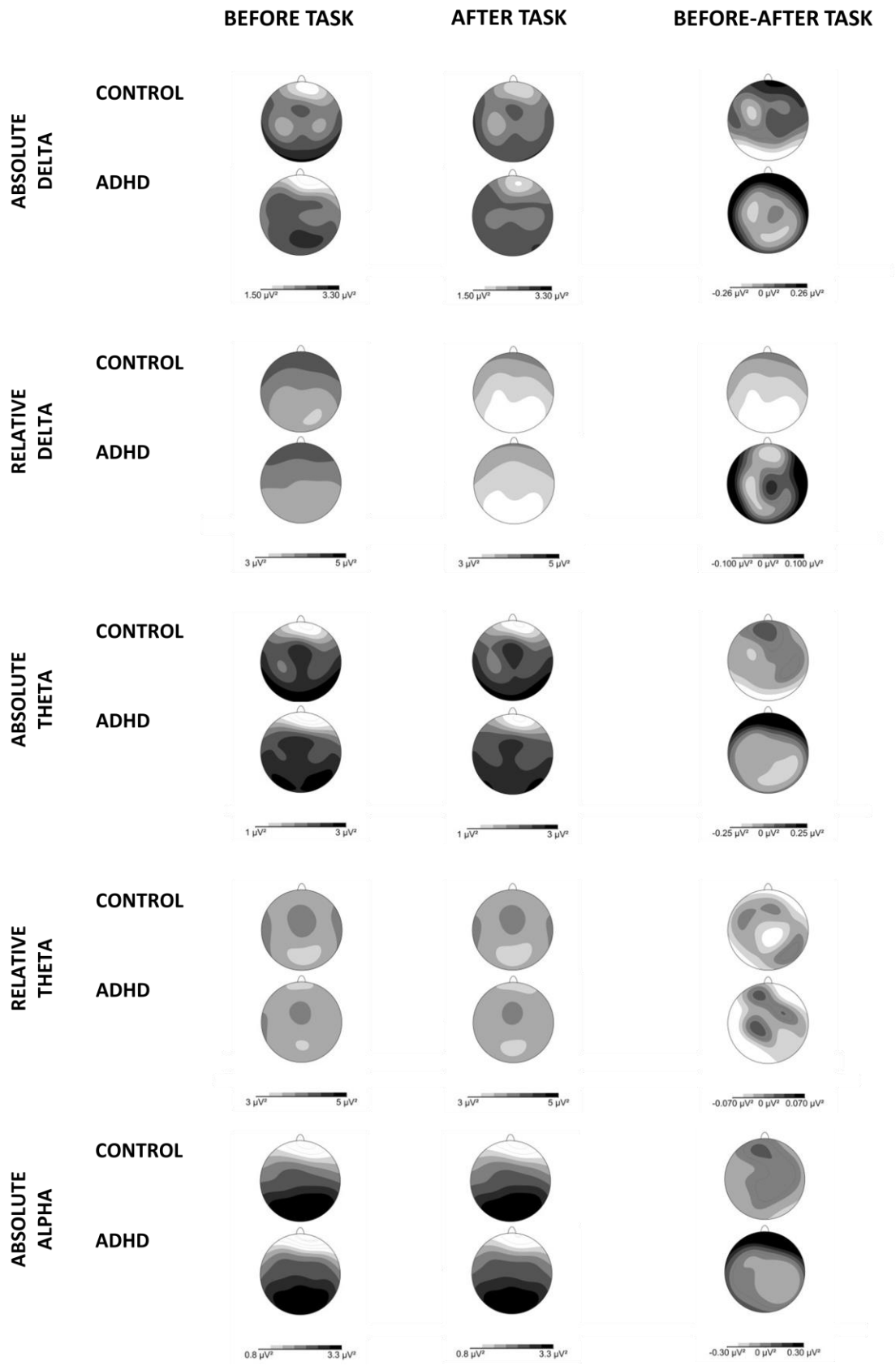
degrees of freedom were corrected using Greenhouse-Geisser (when ε < .75) or Huynh-Feldt (when ε > .75) estimates of sphericity.

Because of the paucity of studies on this topic, not only significant effects but also effects on a subtreshold level of significance (i.e., .05 < *p* < .10) were reported to encourage future research.

RESULTS

The topographic power distributions for resting EEG conditions before and after task execution and the differences in power distribution between conditions for all EEG measures are presented in Figure 1.

The analyses revealed no significant main group effects, nor interaction effects between group and time point for any of the EEG measures. However, some (marginally) significant topographic differences between groups were detected for delta as well as theta and alpha power across resting state conditions. Further, no significant main effects of time point were found in EEG measures or TBR, except for relative theta power, indicating a global decrease of power after task execution in both groups. Additionally, several interaction effects emerged between time point and topographic region in delta, theta and beta frequency bands, indicating local changes in power after task execution in both groups.


BEFORE TASK
AFTER TASK
BEFORE-AFTER TASK
ABSOLUTE DELTA
CONTROL
ADHD
1.50 µV²
3.30 µV²
1.50 µV²
3.30 µV²
-0.26 µV² 0 µV² 0.26 µV²
RELATIVE DELTA
CONTROL
ADHD
3 µV²
5 µV²
3 µV²
5 µV²
-0.100 µV² 0 µV² 0.100 µV²
ABSOLUTE THETA
CONTROL
ADHD
1 µV²
3 µV²
1 µV²
3 µV²
-0.25 µV² 0 µV² 0.25 µV²
RELATIVE THETA
CONTROL
ADHD
3 µV²
5 µV²
3 µV²
5 µV²
-0.070 µV² 0 µV² 0.070 µV²
ABSOLUTE ALPHA
CONTROL
ADHD
0.8 µV²
3.3 µV²
0.8 µV²
3.3 µV²
-0.30 µV² 0 µV² 0.30 µV²

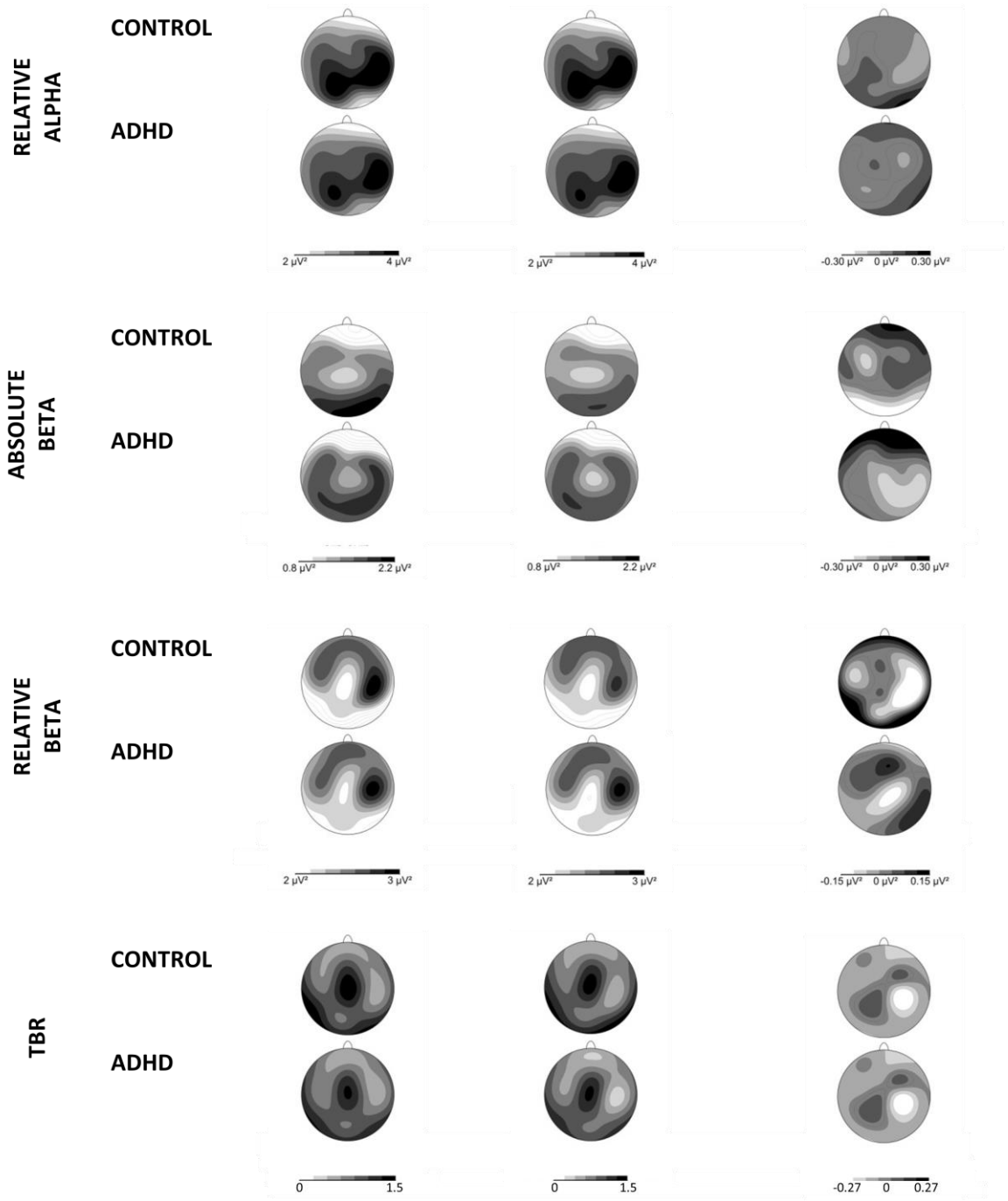


Figure 1. Spectral analysis for conditions before and after task execution. Absolute and relative power for delta, theta, alpha and beta frequency bands (lnμV²) and TBR (theta/beta ratio) (ln). Differences between conditions.

Delta power

A marginally significant interaction between group and lateral region was found for absolute delta power ($F(2, 82) = 2.52$, $p = .09$, $\eta^2_p = .06$). Group divergence did not reach significance at either midline or lateral regions, as indicated by post hoc analyses in the separate lateral regions. Yet, analyses in the separate groups revealed that power across resting state conditions was significantly higher at midline than at lateral sites for typically developing children ($p < .01$ for left and $p < .05$ for right region) but not for children with ADHD ($p = 1.00$ for left and $p = .76$ for right region). For relative delta power, a trend to significant effect was detected between group and sagittal region ($F(1.66, 68.02) = 2.82$, $p = .08$, $\eta^2_p = .07$). Post hoc analyses yielded no significant group differences in either frontal, central or posterior region. Within-subjects contrasts demonstrated that the topographic progressive attenuation of delta power from anterior to posterior sites was larger in control children than in children with ADHD, be it only on a marginally significant level ($F(1, 41) = 3.67$, $p = .06$, $\eta^2_p = .08$).

Further, an interaction between time point and sagittal position emerged in both absolute ($F(2, 82) = 3.20$, $p < .05$, $\eta^2_p = .07$) and relative delta ($F(2, 82) = 3.40$, $p < .05$, $\eta^2_p = .08$). Post hoc analyses revealed a posterior decrease in absolute power ($F(1, 41) = 4.64$, $p = .04$, $\eta^2_p = .10$) and a central increase in relative delta power after task execution ($F(1, 41) = 5.54$, $p < .05$, $\eta^2_p = .12$).

Theta power

The topographic group effects that emerged in theta power were analogous to the effects in delta power. That is, the marginally significant interaction between group and lateral region ($F(2, 82) = 2.57$, $p = .08$, $\eta^2_p = .06$) for absolute theta power indicated that theta was significantly higher for controls ($p < .001$ for both lateral sites) but not for ADHD at midline than at lateral sites ($p = 1.00$ for left and $p = .23$ for right region) across

resting state conditions. Also, the interaction effect between group and sagittal region for relative theta power ($F(1.43, 58.44) = 3.30$, $p = .06$, $\eta^2_p = .08$) demonstrated that the power diminishment from anterior to posterior sites tended to be larger in control children than in children with ADHD ($F(1, 41) = 3.56$, $p = .07$, $\eta^2_p = .08$).

In addition, an interaction between time point and sagittal position emerged in absolute theta ($F(1, 41) = 4.57$, $p = .01$, $\eta^2_p = .10$), indicating a significant posterior ($F(1, 41) = 7.84$, $p < .01$, $\eta^2_p = .16$) and a marginally significant central reduction ($F(1, 41) = 3.02$, $p = .09$, $\eta^2_p = .07$) of absolute theta power after task execution. Further, these focal reductions in absolute theta power led to a trend for a global decrease in absolute theta power after cognitive effort ($F(1, 41) = 3.92$, $p = .05$, $\eta^2_p = .09$). As for relative measures, a significant global reduction was found for theta power after task execution ($F(1, 41) = 5.89$, $p = .02$, $\eta^2_p = .13$).

Alpha power

For absolute alpha power, a marginally significant interaction between group and sagittal region emerged ($F(1.83, 75.08) = 3.07$, $p = .06$, $\eta^2_p = .07$), an effect which reached significance in relative alpha activity ($F(2, 82) = 4.67$, $p = .01$, $\eta^2_p = .10$). Post hoc tests revealed no significant group differences in either sagittal region. However, within-subjects contrasts demonstrated a larger progressive expansion from anterior to posterior sites in absolute ($F(1, 41) = 4.03$, $p = .05$, $\eta^2_p = .09$) as well as in relative ($F(1, 41) = 6.89$, $p = .01$, $\eta^2_p = .14$) alpha power in the control group relative to the ADHD group.

No significant effects involving time point were detected in absolute as well as relative alpha power.

Beta power

Topographic distribution of both absolute and relative beta power did not significantly differ between groups.

The significant interaction between time point and sagittal region in absolute beta ($F(2, 82) = 6.18$, $p < .01$, $\eta^2_p = .13$) power indicated a posterior ($F(1, 41) = 5.86$, $p = .02$, $\eta^2_p = .13$) and central reduction ($F(1, 41) = 5.07$, $p = .03$, $\eta^2_p = .11$) of absolute beta power after task execution. As for relative beta power, a significant interaction emerged between time point and sagittal region ($F(2, 82) = 3.34$, $p < .05$, $\eta^2_p = .08$). Post hoc analyses revealed that relative central beta power tended to reduce ($F(1, 41) = 3.13$, $p = .08$, $\eta^2_p = .07$) after cognitive effort.

TBR

TBR did not differentiate between groups and time points.

Additional analyses with age and sex as covariate

Separate additional analyses with sex and age as a covariate, marginally changed group related results in alpha power. That is, the level of significance of the interaction between group and sagittal region for absolute alpha slightly increased with sex or age as a covariate (*p*-levels going from $p = .06$ to $p = .04$ for both covariates; effect sizes going from $\eta^2_p = .07$ to $\eta^2_p = .08$). When age was taken into account, the group x sagittal region effect in relative theta power slightly increased (*p*-levels going from $p = .06$ to $p < .05$, effect sizes remained $\eta^2_p = .08$). However, given the small groups, and therefore reduced power, it might be more appropriate to evaluate the changes in the analyses with covariates according to effect sizes rather than to *p*-levels. Hence, additional analyses with these covariates showed that the effect sizes remained categorised as medium effects.

DISCUSSION

The present study was set out to investigate whether plausible EEG deviances, particularly enhanced theta power and increased TBR, are a stable characteristic of children with ADHD across eyes closed resting conditions before and after cognitive effort or whether discrepancies may be context or state dependent.

Across conditions, no higher theta power or elevated TBR was observed in children with ADHD relative to typically developing children. Also, groups were not found to diverge in terms of higher or lower power values in delta, alpha and beta frequencies. Yet, across resting conditions, a significant larger topographic expansion from anterior to posterior sites was detected in absolute and relative alpha power in typically developing children compared to children with ADHD. Also, the control group demonstrated a larger sagittal diminution from anterior to posterior sites in relative delta and theta power, although this effect did not reach an acceptable significance level. Further, the midline distribution in absolute theta and delta power tended to be higher in typically developing children compared to children with ADHD. With respect to state-related effects following task execution, a global reduction of relative theta power and an attenuation in absolute delta, absolute theta and absolute beta power at posterior sites were detected in both groups, as well as a decrease in central beta power and an increase in central relative delta power. Yet, no evidence was found for altered state-related changes in EEG after task execution in ADHD.

The findings of the present study disaccord with frequently reported elevated theta power or increased TBR in other studies (for a review, see Barry et al., 2003; Clarke et al., 2007; Clarke et al., 2011; Dupuy et al., 2011; Lansbergen et al., 2011; Loo et al., 2010; Shi et al., 2012). However, our results are in line with some recent studies (Coolidge et al., 2007; Liechti et al., 2013; Loo et al., 2013; Nazari et al., 2011; Ogrim et al., 2012; Swartwood et al., 2003) that also failed to replicate these abnormalities.

Findings regarding delta, alpha and beta power are not surprising since deviances in those EEG rhythms in ADHD have not consistently been established across publications (see introduction). As for the absence of finding reduced beta power or elevated TBR in the ADHD group, one may argue that these deviances were not detected because our sample comprised a subgroup of children with ADHD showing excessive beta power (Clarke, Barry, McCarthy, & Selikowitz, 2001c). However, additional analyses in this respect revealed that this was not the case. In comparison to other studies (for an overview, see Arns et al., 2013; Liechti et al., 2013), non-logaritmic transformed TBRs at the vertex in the present study are in the range of published TBRs for both groups. Yet, they approach the maximum for the controls, and the minimum published values for the ADHD groups compared to other publications. These findings align with the identification of a decreasing difference in TBR in children with ADHD relative to control groups across studies in the last decade (Arns et al., 2013). Poor distinction between groups on a behavioural level is most probably also not a confounder in the present study, since severe inclusion criteria were used in both groups, resulting in highly distinguishable groups in terms of the presence of ADHD symptoms as determined in the DBD Rating Scale. Nevertheless, it is plausible that differences in the make-up of the sample may have contributed to divergent findings across studies (Arns et al., 2013; Liechti et al., 2013). Our ADHD sample comprised children with ADHD inattentive subtype (i.e., 9) as well as combined (i.e., 11) and hyperactive-impulsive (i.e., 1) subtype, which may have played a role. Regarding EEG differences between ADHD subtypes, some studies were not able to detect EEG divergence between ADHD subtypes, while others reported more aberrant EEG activity in one subtype relative to the other and/or the control group (Buyck & Wiersema, 2014; Clarke et al., 1998, 2001b; Dupuy et al., 2011; Hermens et al., 2004; Loo et al., 2010). Unfortunately, reliable examination of EEG divergence according to ADHD subtypes is hampered by the size of our sample, yet this calls for further research. In addition, the presence of comorbid disorders in the ADHD

groups, which is actually rather a rule than an exception, may also serve as an explaining factor for diverse results between studies. Although the influence of comorbidity on resting EEG findings in ADHD has not been investigated systematically, a recent study points to possible mediating effects of oppositional defiant disorder (ODD)/conduct disorder (CD) and depressive disorder in deviance in TBR in ADHD (Loo et al., 2013). As for the present study, 5 children with ADHD were diagnosed with comorbid ODD, one of them also received a diagnosis of CD. More studies with larger sample sizes are needed to evaluate the impact of comorbidity on resting EEG findings in ADHD. Another factor that might be relevant in explaining the absence of aberrant theta power and TBR is the relatively high number of girls (i.e., male to female ratio approximately 2:1) adopted in the current study. Some evidence has been found for smaller EEG differences between girls relative to boys with ADHD and typically developing children (for a review, see Dupuy et al., 2013), yet it has also been documented that enhanced TBR in ADHD is not affected by sex (Monastra et al., 1999). Moreover, some studies evaluating only females have reported increased slow wave activity and/or an elevated TBR (Clarke et al., 2003; Dupuy et al., 2011) in girls with ADHD. In addition, controlling for sex in our analyses appeared not to contribute largely to changing group results. Hence, the absence of EEG abnormalities in children with ADHD is most likely not due to a gender-related factor, but future studies are warranted that systematically investigate this issue. Finally, in the current study, both children with ADHD who take or do not take stimulants in daily life have been incorporated. This factor also differs between studies, with some investigating only medication naïve patients (e.g., Clarke et al., 2008), while most others examining both children who are on and off medication in daily life (e.g., Shi et al., 2012). Studies exploring the effects of stimulant medication on brain wave activity have indicated that the intake of stimulants results in a decrease in theta power (Loo, Teale, & Reite, 1999; Clarke et al., 2003; Clarke, Barry, McCarthy, Selikowitz, & Johnstone, 2007) and TBR (Clarke, Barry, McCarthy, Selikowitz, & Croft, 2002b). However, in the present

study medication use was controlled for by requiring a wash-out period of 48 hours for children who used medication in daily life. Consequently, we doubt that medication use in a part of our ADHD sample may have been a confounding factor, although future studies investigating long-term medication effects on resting EEG in ADHD are recommended.

Although the findings of the present study do not confirm the typically observed aberrant theta power and TBR in ADHD in other studies, divergence in topographic distribution of EEG activity on the sagittal plane was found for alpha power with a smaller expansion from anterior to posterior sites in children with ADHD. Importantly, this cannot be explained by the children with ADHD incidentally opening the eyes during the recordings, while an experimenter monitored the children during the experiment. We are not aware of any study that examined linear within subjects contrasts in deviation between groups, which impedes comparison of our observation of smaller changes in EEG distribution from anterior to posterior sites in alpha to other studies. Also, to our knowledge, no publications are available regarding the significance of the topographic pattern of EEG activity between different regions. Even so, it is well known that during resting state, the brain attempts to preserve a physiological and functional balance. In order to do so, different local and long-range cortical neural activities co-occur and may interact with each other (Woltering, Jung, Liu, & Tannock, 2012). Variations in topographic distribution in ADHD may therefore reflect deficient neural communication or the use of different underlying sources of activity, which may be related to ADHD symptomatology. While the results of the present study are suggestive of possible different topographic distribution between ADHD and controls, before drawing further conclusions on this, studies involving a larger number of participants will be needed to confirm generalizability of the results. Despite this limitation, other studies investigating a similar widespread topographic distribution in ADHD also point to deviance between groups depending on examined region (e.g., Clarke et al., 1998;

2001), which underlines the importance of investigating widespread cortical activity in ADHD and not limiting EEG comparison between groups to a small number of electrode derivations.

As for EEG changes after cognitive effort, the present findings confirm that intervening task execution results in modified resting EEG patterns after effort, be it similarly in both groups. The most consistent finding in studies that have examined EEG before and after task execution has been an increase in theta rhythm following cognitive effort (Smit et al., 2004, 2005; Tanaka et al., 2012), which has traditionally been accounted for by mental fatigue. A theta increase after cognitive effort was not replicated in the present study, in which instead a decrease in theta power was detected. It may be argued that performing n-back tasks for only 40 minutes may not have been sufficient to induce mental fatigue and therefore an increase in theta power has not been generated. Previous research has documented that task difficulty may also interfere with the appearance of EEG changes after task execution, suggesting that less demanding tasks elucidate smaller EEG changes (Tanaka et al., 2012). The 0-back tasks used in the present study were not highly demanding in terms of workload, which could therefore also explain the failure to find a theta increase after task performance. This however does not explain the decrease in theta power after task execution as noticed in our study. Yet, modulation in the theta frequency band has not only been associated with a possible reflection of fatigue or task difficulty but also with attentional processing. Although tentative, in accord with research on the effects of meditation on EEG activity relating higher theta power to enhanced attention to internal events (for reviews, see Chiesa & Serretti, 2010; Rubia, 2009), the present finding of a reduction in theta power after cognitive effort may perhaps be the result of participants being more in a state of external focussed attention after task execution than during the baseline resting condition. As for the decrease in beta power after task execution, this is in line with findings of the study by Tanaka and colleagues (2012). Since beta waves are

generally associated with increased attentional arousal (Loo & Makeig, 2012), decreases in beta power after task execution may reflect reduced alertness and attentional processing. Noteworthy is that the EEG changes after task execution were most pronounced at posterior sites. Remarkably, several positron emission tomography and functional magnetic resonance imaging studies have elucidated involvement of the parietal cortex in the performance of spatial tasks (Corbetta, Miezin, Shulman, & Petersen, 1993; Coul & Nobre, 1998; Nobre et al., 1997, 2004; Nobre, 2001). The observed EEG changes after task execution in the current study may therefore possibly reflect altered activity in the parietal cortex, after this brain area has been activated during task performance. Yet, given the relatively poor spatial sensitivity in EEG, carefulness is warranted in this interpretation. However, this hypothesis may also explain why EEG modulation after cognitive effort has been found to differ across studies. That is, since involvement of different brain areas is required during a variety of tasks, this possibly will be reflected in varying topographic distribution of EEG changes after cognitive effort. This may also imply that, although not detected in the present study, there is still potential to elucidate group divergence in EEG modulation after task execution when different tasks, tapping other brain related processes that possibly more discriminate between patients and controls, are used between EEG measurements.

Although not controlled for in the present study, other factors may also contribute to changes in EEG activity after cognitive effort, such as feeling more at ease at the end of the session compared to at the start of the experiment. Both theta and beta (Knyazev, Savostyanov, & Levin, 2005), as well as delta power (Knyazev, 2012), have been associated with feelings of anxiety and uncertainty. Consequently, it is recommended that future studies incorporate additional measures to assess the significance of the induced alteration in state after cognitive effort, since the interpretation regarding the significance of the EEG changes after cognitive effort remains difficult. For instance, questionnaires can be used to detect fatigue or changes

in emotion/motivation after cognitive effort and a well-established measure of autonomic arousal (i.e., skin conductance level, Barry et al., 2009) could assist in detecting possible arousal differences before and after task execution. Furthermore, it could also be of value to control for possible circadian influences in future studies, since these have been demonstrated to affect EEG (Sannita, 2006). Unfortunately, we were not able to do so in the current study as we were dependent on the schedule of the children and their parents to conduct the experiment. That is, children were assessed after school hours or during weekends, taking into account the feasibility of refraining from medication.

Our hypothesis regarding possible state-related factors associated with EEG deviance in ADHD has not been confirmed by the current study design. However, leaving open that task duration or requirement of mental effort were not sufficient to induce altered state-related EEG changes in ADHD, we believe prudence is called for interpretation of these results. There is ample evidence for state related deficits in ADHD on a behavioural, performance, and psychophysiological level (e.g., Metin et al., 2012; Sonuga-Barke et al., 2010; Wiersema et al., 2006a,b), and findings from studies on eyes open versus eyes closed EEG suggest that this may also be the case for quantitative EEG measures (e.g., Fonseca et al., 2013; Liechti et al., 2013). Hence, more research is definitely needed on the influence of state and contextual factors on resting EEG in ADHD.

To conclude, the findings of the present study do not confirm the validity of deviances in theta and TBR characterizing the whole ADHD group, which is in line with a growing number of studies. However, divergences in topographic organization of EEG activity between groups were detected, and therefore, examining widespread cortical activity is recommended in evaluating EEG in ADHD. Finally, the results suggest that time point of EEG measurement did not influence group differences, arguing against

state-related EEG deviances in ADHD, though more research studying context dependency of quantitative EEG measures in ADHD is recommended.

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CHAPTER 4

STATE-RELATED EEG DEVIANCES IN ADHD[1]

ABSTRACT

Objective: This study investigated the stability and state-related characteristics of EEG deviances in ADHD. **Methods:** Three minutes resting EEG with eyes closed and eyes open were compared between 21 children with ADHD and 29 typically developing children. **Results**: Across resting conditions, children with ADHD exhibited divergent topographic distribution for theta, alpha and beta power compared to typically developing children. In addition, less alpha and theta suppression to eye opening was found in children with ADHD, but only in those without comorbid ODD/CD. **Conclusions:** Findings of the present study refer to a consistent divergence in topographic distribution in ADHD across resting state conditions, yet demonstrate that state-related factors and comorbidity may also contribute to resting EEG deviances in ADHD. The state-related findings are in accord with several theoretical accounts emphasizing the role of contextual and state factors defining deficits in ADHD.

[1] Based on Buyck, I., & Wiersema, J.R. (2014). *State-related electroencephalographic deviances in attention deficit hyperactivity disorder.* Manuscript submitted for publication.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder, affecting an estimated 5 to 7 % of the worldwide population (Willcutt, 2012), and is characterized by varying age-inappropriate levels of inattention and/or hyperactivity/impulsivity, leading to impairment in multiple life domains (American Psychiatric Association, 2013). Although the mechanisms are not fully understood, it has often been claimed that ADHD is associated with a dysfunction in the central nervous system (CNS), which has frequently been investigated by means of electroencephalography (EEG).

Resting EEG studies with either eyes closed or open typically have reported increased theta power or an elevated proportion of slow to fast frequency power, theta/beta ratio (TBR), in children with ADHD compared to typically developing children (e.g., Barry, Clarke, & Johnstone, 2003; Dupuy, Clarke, Barry, McCarthy, & Selikowitz, 2011; González-Castro, Rodríguez, López, Cueli, Álvarez, 2013; Lansbergen, Arns, van Dongen-Boomsma, Spronk, & Buitelaar, 2011; Loo et al., 2010; Snyder et al., 2008; Shi et al., 2012). However, lately the robustness of these EEG deviances characterizing the whole ADHD population has become the focus of a debate, as a number of studies, mainly addressing eyes open resting EEG, could not invariably distinguish children with ADHD from a typically developing group based on theta power or TBR (Coolidge, Starkey, & Cahill, 2007; Liechti et al., 2013; Loo et al., 2013; Nazari, Wallois, Aarabi, & Berquin, 2011; Ogrim, Kropotov, & Hestad, 2012; Swartwood, Swartwood, Lubar, & Timmermann, 2003). This also appears to find support by a recent meta-analysis, revealing less discrepancy in eyes open TBR between children with and without ADHD in recent studies compared to earlier studies (Arns, Conners, & Kraemer, 2013). In addition, in a recent study, eyes closed theta activity was observed to be enhanced in 60%, yet reduced in 40% of children with ADHD (Clarke et al., 2011). EEG findings regarding brain wave activity in the faster frequency bands appear to be even more

mixed. That is, although some studies have documented decreased beta (Clarke, Barry, McCarthy, & Selikowitz, 1998; Clarke, Barry, McCarthy, & Selikowitz, 2002a; Clarke et al., 2003; Dupuy et al., 2011; Shi et al., 2012), others have reported increased beta power in a subgroup of children with ADHD (Chabot & Serfontein, 1996; Clarke et al., 1998; Clarke, Barry, McCarthy, & Selikowitz, 2001a) or failed to find group differences in beta power (Liechti et al., 2013; Loo et al., 2010). Likewise, alpha power has often been reported to be reduced in children with ADHD (Barry, Clarke, Johnstone, McCarthy, & Selikowitz, 2009; Clarke et al., 1998; Clarke et al., 2001a, 2003; Dupuy et al., 2011), but has also been found to be enhanced (Chabot & Serfontein, 1996; Clarke et al., 2011), or equivalent to that of typically developing children (Loo et al., 2010; Shi et al., 2012). Various factors may have contributed to the apparent discrepant findings between studies, including sample characteristics and resting state condition in which EEG was recorded (i.e., eyes open or closed). ADHD presents a heterogeneous clinical expression with different subtypes, often comorbid with other conditions such as oppositional defiant disorder (ODD) or conduct disorder (CD). These sample characteristics may vary across studies and although not often taken into account, available research indicates that these may mediate EEG deviances in ADHD (e.g., Buyck & Wiersema, 2014; Clarke, Barry, McCarthy, & Selikowitz, 2002b; Loo et al., 2013). Studies also differ in the resting state condition in which EEG was recorded. Crucially, in order to consider EEG deviances as a trait-like hallmark of ADHD, there should be stability in these abnormalities across different states. Although several studies have demonstrated intra-individual stability of EEG in typically developing children over time (e.g., Fein, Galin, Yingling, Johnstone, & Nelson, 1984; Gasser, Bacher, & Steinberg, 1985), brain oscillations also have been found to be affected by contextual and state factors, such as opening of the eyes (e.g., Barry, Clarke, Johnstone, Magee, & Rushby, 2007; Karhu, Könönen, Herrgård, & Partanen, 1996; Ristanovic, Martinovic, & Jovanovic, 1999; Samson-Dollfus, & Goldberg, 1979). Opening of the eyes has been related to an increase in arousal (Barry et al., 2007;

Hüfner et al., 2009). Interestingly, although some recent studies challenge this account (Barry et al., 2009; Clarke et al., 2013), one of the dominant theories explaining the most consistent EEG deviances in ADHD (i.e., aberrant theta and TBR) have interpreted the abnormalities as hypoarousal of the CNS (for reviews, see Barry et al., 2003; Barry & Clarke, 2009). This raises the question whether a change in arousal state with eye opening is an important factor that should be taken into account in characterizing EEG deviances in ADHD.

So far, most EEG studies on ADHD have focussed on evaluating EEG in either an eyes closed or an eyes opened resting condition, with only a few addressing both resting conditions (Fonseca, Tedrus, Bianchini, & Silva, 2013; Lansbergen et al., 2011; Liechti et al., 2013; Loo et al., 2009, 2010, 2013; van Dongen-Boomsma et al., 2010; Woltering, Jung, Liu, & Tannock, 2012). Interestingly, some of these latter studies reported that deviances in TBR in children (Lansbergen et al., 2011) or adults (Loo et al., 2013) with ADHD were detected in the eyes closed but not in the eyes open condition. Hence, these findings suggest that, whether or not the EEG profile in ADHD is aberrant, it may depend on arousal state. The notion that state factors may play a role when investigating resting EEG in ADHD is further supported by findings of group differences in EEG reactivity to opening or closing the eyes. That is, studies have demonstrated reduced frontal and/or posterior alpha suppression to opening the eyes in children as well as adults with ADHD (Fonseca et al., 2013; Loo et al., 2010; Woltering et al., 2012), but see Loo et al., 2009, van Dongen-Boomsma et al., 2010. Also, a greater theta power increase to closing the eyes has been observed in children with ADHD (Liechti et al., 2013). Although studies that investigated resting EEG in ADHD during different arousal states are scarce, the findings seem to highlight a state-related factor in EEG deviances in ADHD. Interestingly, these results are in line with several theoretical frameworks that emphasize the role of contextual and state factors instead of fixed factors in defining deficits in ADHD, such as the state regulation deficit model (Sergeant, 2005; van der

Meere, 2005) and the delay aversion model (Sonuga-Barke, Taylor, Sembi, & Smith, 1992), which emphasize respectively dynamic underlying failures of energetic state or motivational factors in ADHD (Sonuga-Barke, Wiersema, van der Meere, & Roeyers, 2010).

To gain further insight into the role of state-related factors (i.e., arousal) in determining EEG deviances in ADHD, in the current study, EEG activity in an eyes closed and eyes open resting condition will be compared between children with ADHD and typically developing children. Although most studies on ADHD address sagittal topographical differences in EEG reactivity following eye opening, to our knowledge EEG differences between groups on the lateral plane (i.e., left hemisphere, midline and right hemisphere) have hardly been investigated. Yet, this may be important, since a few studies documented hemispherical divergence in EEG activity in ADHD (Hale et al., 2009, 2010a, 2010b; Keune et al., 2011). Therefore, in the present study, sagittal as well as lateral scalp regions were included, enabling a thorough investigation of possible topographical differences between groups and conditions. Furthermore, as only a few studies on EEG reactivity in ADHD have systematically addressed a wide range of EEG frequencies and TBR, brain wave activity from theta to beta frequency bands and TBR related to eye opening will be evaluated.

If elevated theta power and TBR are trait-like markers of ADHD, then increased theta power and TBR are expected in both resting state conditions. An interaction effect between group and resting state condition would indicate that state factors are associated with EEG abnormalities in ADHD. In line with literature findings, the largest differences are expected in the eyes closed condition. In addition, based on previous reactivity studies, children with ADHD are hypothesized to show less alpha suppression when opening the eyes.

METHOD

Participants

Participants were 22 children with ADHD and 29 typically developing children between 7 and 14 years old with an estimated full scale IQ of 80 or higher (Table 1), which were recruited through advertisements, schools, and staff members. Children with ADHD were furthermore referred by child neurologists. Participants with ADHD were previously diagnosed with ADHD in a clinical setting according to criteria as specified in DSM-IV. ADHD-diagnosis was confirmed by administering the parent version of the behavioral module of the Diagnostic Interview Schedule for Children IV (DISC-IV) (Schaffer, Fisher, Lusac, Dulcan, & Schwab-Stone, 2000). Disruptive Behavior Disorder Rating Scale (DBD-RS) (Pelham, Gnagy, Greenslade, & Milich, 1992) and Child Behavior Checklist (Achenbach & Rescorla, 2001) were used to evaluate respectively ADHD symptoms and possible presence of psychiatric problems in both groups. Intelligence functioning was assessed by an abbreviated Wechsler Intelligence Scale for Children-III (Wechsler, 1991; Grégoire, 2000). Exclusion criteria for participation consisted of a history of brain related illness, neurological disorder, serious medical condition, learning disorder, and autism spectrum disorder. Children from the control group were required to reach scores below clinical cut off on DBD-RS and Child Behavior Checklist (CBCL) (Achenbach & Rescorla, 2001). One child with ADHD had to be excluded from the analyses as it received a diagnosis of autism spectrum disorder during the study. This resulted in an ADHD group comprising 9 children of the predominantly inattentive type, 1 child of the predominantly hyperactive/impulsive type and 11 children of the combined type. 4 children with ADHD also met criteria for ODD, 1 child met criteria for both ODD and CD, as determined by the DISC-IV. Children with ADHD using stimulant medication for ADHD symptoms (i.e., 11 children) were asked to refrain from medication for at least 48 hours before participation in the experiment.

Table 1. Sample characteristics

	CONTROL (*n* = 29)	ADHD (*n* = 21)
Male/female	14/15	13/8
Age in years	*M* 10.46 (*SD* 1.75)	*M* 10.20 (*SD* 1.73)
Estimated FSIQ	*M* 108.10 (*SD* 11.55)	*M* 103.10 (*SD* 12.43)
DBD-RS inattention	*M* 3.31 (*SD* 4.06)	*M* 16.76 (*SD* 4.28)
DBD-RS hyperactivity impulsivity	*M* 3.21 (*SD* 3.41)	*M* 12.81 (*SD* 5.18)
Number of segments EC	*M* 112.72 (*SD* 35.33)	*M* 107.95 (*SD* 33.99)
Number of segments EO	*M* 126.59 (*SD* 33.13)	*M* 105.14 (*SD* 39.75)

Note. *M*: mean, *SD*: standard deviation, FSIQ: Full Scale Intelligence Quotient, DBD-RS: Disruptive Behavior Disorder Rating Scale, EC: eyes closed, EO: eyes open

Procedure

Written informed consent was obtained from parents before their child participated in the experiment, in line with a research protocol approved by the ethic committee of the Faculty of Psychology and Educational Sciences at Ghent University.

Participants first completed the questionnaires, after which the DISC was administered to parents and intelligence of the children was assessed. Electrophysiological registration was planned in another session that comprised neuropsychological testing (not discussed in the current paper) and recording of resting state EEG. For the purpose of the current study, resting EEG from the eyes open and eyes closed condition (3 minutes each) recorded after neuropsychological testing was evaluated. During eyes open resting conditions, participants were instructed to fixate on a white cross that was presented on a black background in the middle of a computer screen. Resting state EEG conditions were counterbalanced across participants. The total session (i.e., the time that was needed for placement of the EEG cap and the execution of the experiment) took about 1.5 hour.

Electrophysiological procedure

Participants were fitted with a 128 electrode cap with 10 mm Ag/AgCl electrodes (EasyCap Active, EasyCap GmbH) placed according to the 10-5 International System (Oostenveld & Praamstra, 2001). Data were collected with a sample rate of 500 Hz and average referenced with the ground electrode mounted within the cap at Fpz. Electro-oculogram was registered through electrodes enclosed in the cap near the eyes. A QuickAmp amplifier (Brain Products, Gilching, Germany) was employed to amplify signals with an open pass-band from direct current to 100 Hz. Brain Vision Analyzer software (version 2.0.1) was used to filter (0.5 Hz to 50 Hz band-pass, notch filter of 50 Hz) and segment (2 s epochs with 1 s overlap) data offline. Ocular artefact correction was conducted according to the Gratton and Coles algorithm (Gratton, Coles & Donchin, 1983). Segments with amplitudes exceeding ±100 μV were removed from further analyses. The remaining number of segments for analyses did not differ between conditions ($F(1, 48) = 1.79$, $p = .19$) and groups ($F(1, 48) = 2.00$, $p = .16$) (Table 1). Spectral power was calculated using Fast Fourier Transform with a 20% Hanning window. For comparison purposes (Barry et al., 2009), absolute power estimates were derived for the theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz) and beta (12.5-25 Hz) band and divided in nine regions: left frontal (AF3, F3, F7), midline frontal (Fz, FCz), right frontal (AF4, F4, F8), left central (T7, C3), midline central (Cz), right central (T8, C4), left posterior (P7, P3, O1), midline posterior (Pz, Oz) and right posterior (P8, P4, O2). Theta/beta power ratio was obtained by dividing the power of the theta band by the power of the beta band. A natural logarithmic transform, ln(x), was applied to approach normal spreading of the data.

Statistical analyses

Eyes closed and eyes open EEG activity in children with and without ADHD were compared by running separate analyses of variance with repeated measures for each

EEG measure with condition (eyes closed, eyes open), sagittal region (frontal, central, posterior) and lateral region (left, midline, right) as within-subject factors and group (ADHD, controls) as between-subject factor. When the assumption of sphericity was violated, degrees of freedom were corrected using Greenhouse-Geisser (when $\varepsilon < .75$) or Huynh-Feldt (when $\varepsilon > .75$) estimates of sphericity. Effect sizes were determined by partial eta squared (η^2_p) and are interpreted as small (< .06), medium (.06 - .14), or large (> .14) (Cohen, 1988).

Since comorbid ODD/CD has been documented to possibly play a mediating role in detecting EEG deviances in ADHD (Clarke et al., 2002b; Loo et al., 2013), a supplementary analysis was performed excluding children with comorbid ODD/CD (i.e., 5/21) (see also Liechti et al., 2013). As age and gender have been demonstrated to affect EEG (e.g., Clarke Barry, McCarthy, Selikowitz, 2001b; Dupuy, Barry, Clarke, McCarthy, & Selikowitz, 2013), separate additional analyses were run with these factors as covariates.

In view of the scope of the present study, only effects involving diagnostic status are discussed. Because of the relative paucity of studies on this topic, not only significant effects but also effects on a subtreshold level of significance (i.e., $.05 < p < .10$) are reported to encourage future research (see also Barry et al., 2004).

RESULTS

Group characteristics

The DBD-RS confirmed that children with ADHD experienced more problems with inattention ($F(1, 48) = 127.76$, $p < .001$) as well as hyperactivity/impulsivity ($F(1, 48) = 62.54$, $p < .001$) than typically developing children. The groups did not significantly differ

in terms of age (F(1, 48) = 0.26, p = .62) and estimated full scale IQ (F(1, 48) = 2.15, p = .15) (Table 1).

EEG analyses

The topographic power distributions for eyes closed and eyes open resting conditions and the differences in power distribution between conditions in each frequency band and TBR are presented in Figure 1.

Theta power. As for theta power, a group-by-lateral region interaction was found (F(2, 96) = 4.40, p = .02, η^2_p = .08), indicating theta power across resting state conditions was higher for controls than for ADHD at midline than at lateral electrode sites. Yet, group differences did not reach significance at either midline or lateral region.

Alpha power. Likewise, a significant interaction between group and lateral region was detected for alpha power (F(2, 96) = 3.77, p = .03, η^2_p = .07). Although groups did not significantly differ in either region, higher alpha power at midline than at lateral sites was detected in the control group but not in the ADHD group.

Beta power. Beta power also differed between groups on the lateral plane (F(2, 96) = 3.52, p = .03, η^2_p = .07). Further testing revealed a greater reduction in power at midline compared to lateral sites in children with ADHD than in typically developing children. Yet, again, no significant differences between groups were detected at either midline or lateral region.

TBR. No significant interaction effects involving group were detected for TBR.

Supplementary analyses with age and sex as a covariate did not change the group related effects for all frequency bands and TBR.

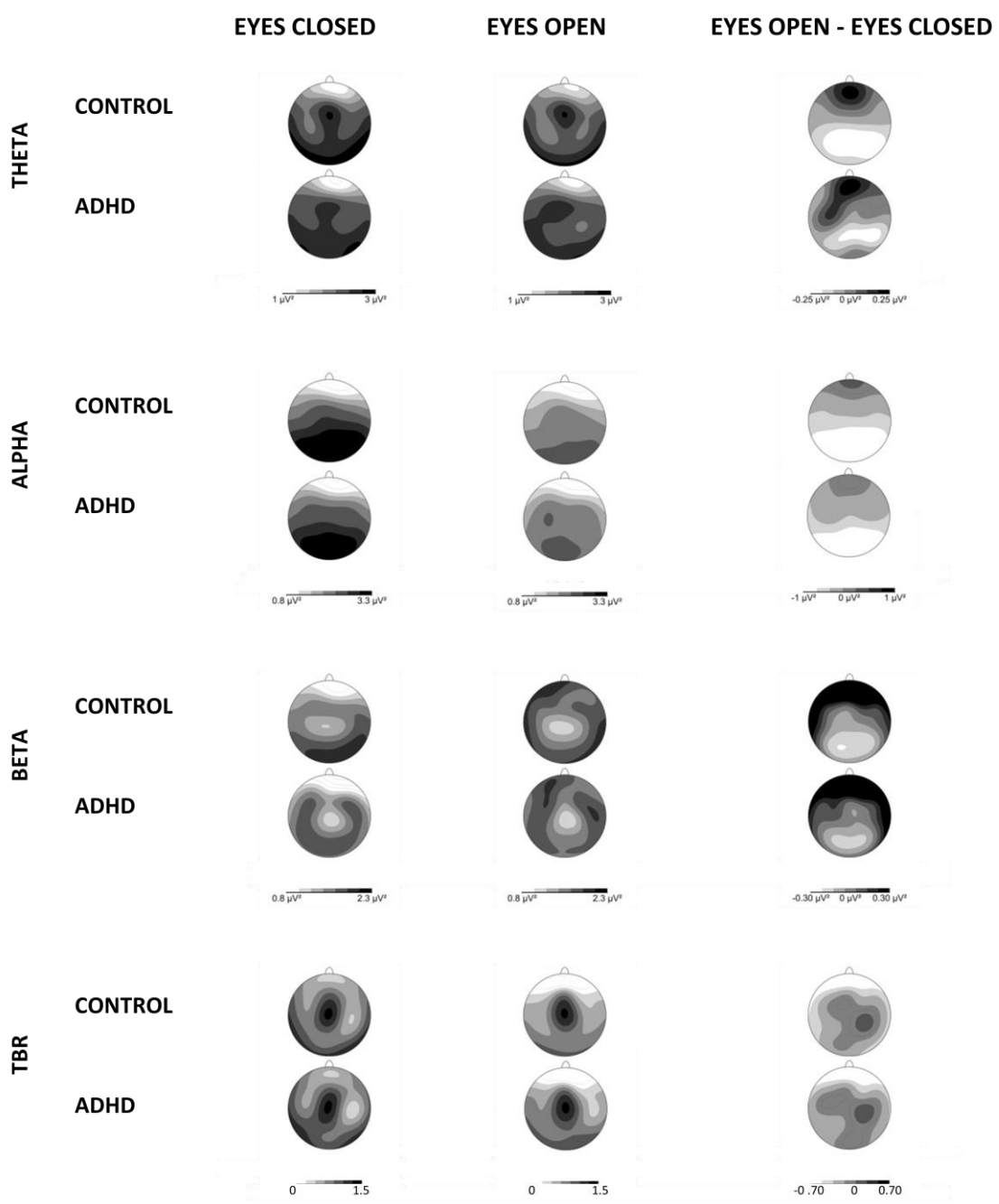

Figure 1. Spectral analysis for eyes closed and eyes open conditions. Absolute power for theta, alpha and beta frequency bands (lnμV²) and TBR (theta/beta ratio) (ln). Differences between eyes open and eyes closed conditions.

Supplementary analyses excluding children with comorbid ODD/CD. Regarding topographic differences between groups, the *p*-levels in alpha and beta power slightly reduced but the effect sizes remained in the same range (respectively $p = .06$, $\eta^2_p = .07$ and $p = .08$, $\eta^2_p = .07$). Since the interpretations of the effect sizes between the analyses with and without children with comorbid ODD/CD were comparable, the slight decreases in *p*-levels probably resulted from the reduction in power following the exclusion of 5 children from the analyses. The significant effect in theta power remained when only children without comorbid ODD/CD were included in the analyses.

Further, excluding children with comorbid ODD/CD from the analyses revealed that topographic distribution on the sagittal plane for alpha power differed between groups ($F(2, 86) = 4.87$, $p = .01$, $\eta^2_p = .10$), indicating a steeper increase from anterior to posterior sites in typically developing children than in children with ADHD ($F(2, 86) = 8.98$, $p < .01$, $\eta^2_p = .17$). In addition, a group-by-condition effect was detected ($F(1, 43) = 5.12$, $p = .03$, $\eta^2_p = .11$) in alpha power, denoting alpha suppression with eye opening was lower in the ADHD group than in the control group. Yet, group differences did not reach significance in either condition. Also, a marginally significant group x condition x sagittal region effect appeared ($F(1.74, 74.83) = 2.75$, $p = .08$, $\eta^2_p = .06$), meaning that the smaller alpha attenuation with eye opening in ADHD was most apparent in central ($F(1, 43) = 8.05$, $p < .01$, $\eta^2_p = .16$) and posterior ($F(1, 43) = 4.56$, $p = .04$, $\eta^2_p = .10$) region (Figure 2).

Furthermore, EEG response to eye opening tended to differ between groups in theta power ($F(1, 43) = 3.43$, $p = .07$, $\eta^2_p = .07$), resulting from a slight theta decrease in the control group ($F(1, 28) = 2.97$, $p < .10$, $\eta^2_p = .10$) which was not apparent in the ADHD group. No group differences in theta power were detected in either condition. Further testing regarding the marginally significant group x condition x sagittal region effect in theta power ($F(1.66, 71.25) = 2.88$, $p = .07$, $\eta^2_p = .06$), revealed that the group difference in EEG reactivity to eye opening was significant in posterior region ($F(1, 43) = 4.59$, $p =$

.04, η^2_p = .10) (Figure 2) and marginally significant in central region (F(1, 43) = 3.57, p = .07, η^2_p = .08).

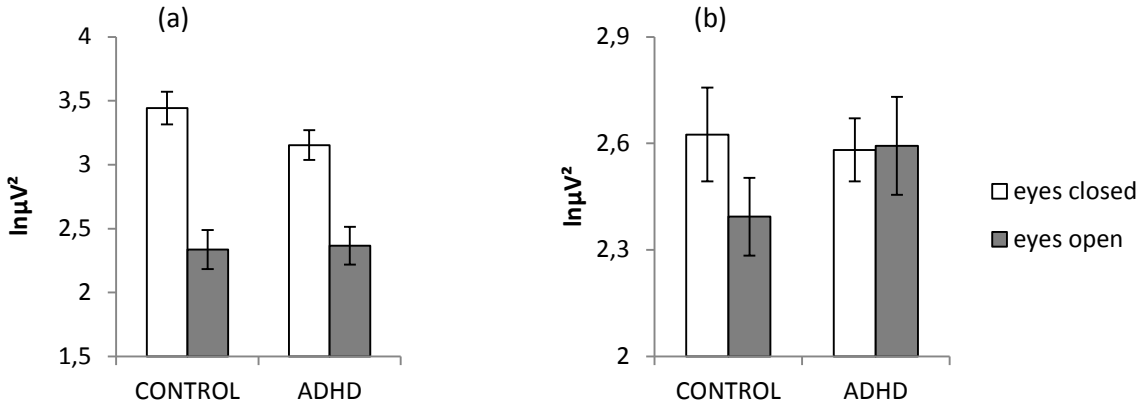

Figure 2. Mean (a) alpha and (b) theta power for posterior sites in eyes closed and eyes open conditions for children with ADHD without comorbid ODD/CD and control children. Error bars represent the standard error of the mean.

DISCUSSION

The present study was set out to investigate the stability and state-related characteristics of EEG deviances in ADHD. While no aberrant theta power and TBR were found in children with ADHD, a divergence in topographic distribution between midline and lateral sites was observed between groups in theta, alpha and beta power across resting conditions. Further, children with ADHD without comorbid ODD/CD exhibited less suppression of central and posterior alpha and theta power with eye opening than typically developing children.

In the current study, more derivations were used to investigate EEG compared to most existing studies, which enabled us to reveal group differences in lateral distribution of EEG activity. The observed midline distribution for theta power in typically developing children highly corresponds with other studies (for a review, see Barry & Clarke, 2009). Findings regarding beta and alpha power are less in line with other

studies, in which a midline distribution for beta power and a more equivalent distribution for alpha power across the lateral plane has been documented in control groups (for a review, see Barry & Clarke, 2009). Although other studies did not report the more equivalent distribution of EEG activity in ADHD that we observed in the present study, they also point to more deviance between groups at midline than lateral regions (e.g., Clarke et al., 1998; Clarke et al., 2001b), which underlines the importance of investigating widespread cortical activity in ADHD. Therefore, it is recommended that future studies investigating EEG deviances in ADHD incorporate a sufficient number of electrodes. The paucity in the literature concerning power distribution across a lateral dimension including the midline, impedes drawing firm conclusions regarding the brain mechanisms underlying the deviances between children with ADHD and typically developing children. Nevertheless, during resting state, preservation of a physiological and functional balance in the brain relies on different local cortical neural activities and long-range corticocortical/cortico-subcortical neural activities that coexist and may interact with each other (Woltering et al., 2012). Variations in topographical distribution in ADHD may therefore reflect deficient neural communication or dysfunction in distributed network organization (for a review, see Konrad & Eickhoff, 2010), which may be related to ADHD symptomatology. Before drawing further conclusions on this, the robustness of the current findings should be replicated in future research.

Still, our findings regarding comparable theta and TBR between groups are in contrast with other studies (Barry et al., 2003; Clarke et al., 2007; Clarke et al., 2011; Dupuy et al., 2011; González-Castro et al., 2013; Lansbergen et al., 2011; Loo et al., 2010; Snyder et al., 2008; Shi et al., 2012), but correspond with some recent studies that also failed to replicate increased theta or TBR in ADHD (Coolidge et al., 2007; Liechti et al., 2013; Loo et al., 2013; Nazari et al., 2011; Ogrim et al., 2012; Swartwood et al., 2003). As for alpha and beta power, our results are not unexpected since deviances in

those frequency ranges in ADHD have not been consistently observed across studies (see introduction).

Among others, it is plausible that differences in sample characteristics for both children with and without ADHD may have contributed to divergent findings across studies (Arns et al., 2013; Liechti et al., 2013). Regarding sex, it has been suggested that boys have different EEG abnormalities than girls with ADHD (for a review, see Dupuy et al., 2013). In the current study, more girls were included in the control group than in the ADHD group. Furthermore, the proportion of boys to girls in our ADHD sample was somewhat lower than in most studies (e.g., Shi et al., 2012). However, higher theta or TBR in ADHD has been detected in samples with even a smaller boy to girl ratio than in the current study (e.g., Clarke et al., 2001b; Loo et al., 2010). Moreover, controlling for sex in our analyses did not change the results. Therefore, we cautiously conclude that sex did not act as a confounding factor. Our study included children with ADHD with different subtypes and it may be that enhanced theta or TBR is only related to one of these subtypes. However not much research has been done on EEG differences between ADHD subtypes and so far disparate findings have been reported, with some studies documenting comparability in EEG activity between ADHD subtypes, and others observing more pronounced quantitative EEG differences in one subtype relative to the other and/or the control group (Buyck & Wiersema, 2014; Clarke et al., 1998; Clarke et al., 2001b; Loo et al., 2010; Dupuy et al., 2011). Unfortunately, the size of our sample impedes reliable investigation of divergence according to ADHD subtypes, yet this could be further explored in future work. Furthermore, in the current study, 11 children with ADHD were on stimulant medication in daily life. Studies addressing the impact of stimulant medication on brain wave activity have indicated a power decrease in the theta band (Loo, Teale, & Reite, 1999; Clarke, Barry, McCarthy, Selikowitz, & Johnstone, 2007) and a reduction in TBR (Clarke, Barry, Bond, McCarthy, & Selikowitz, 2002c) following medication. Although we are not aware of studies investigating the specific

duration of medication effects on EEG activity, a medication wash-out period of 48 hours was respected, which is even more restrictive than regular research procedures across EEG studies (e.g., Loo et al., 2010) in ADHD. Consequently, we do not regard daily medication use in a part of our ADHD sample as a confounding factor for our results, yet further research may be warranted investigating (long-term) effects of daily life use of stimulants on EEG in ADHD.

Another source of heterogeneity in ADHD samples across studies refers to the presence of comorbid disorders. It is well established that a large proportion of children with ADHD has at least one comorbid psychiatric diagnosis, with ODD occurring the most frequently (Biederman, 2005). Yet, often studies have not controlled for comorbid ODD/CD and research on how this comorbidity influences EEG in ADHD is scarce. One study has documented that comorbidity with ODD/CD possibly enlarges TBR deviance in children with ADHD (Loo et al., 2013), while another study did not detect this effect and instead reported that focal theta abnormalities were more pronounced in an ADHD only group than in an ADHD group with ODD/CD comorbidity (Clarke et al., 2002b). However, both studies focussed on an eyes closed resting condition only and were therefore not able to address the influence of comorbid ODD/CD on EEG response to eye opening. In the present study, although no divergence was found in the separate resting state conditions, group differences in alpha and theta reactivity on eye opening emerged when excluding children with comorbid ODD/CD, alluding more deviance in children with pure ADHD (i.e., not suffering from comorbid disruptive behavior disorder). Currently, the debate is still ongoing whether comorbid oppositional symptoms in ADHD should be considered as a component of ADHD or whether ADHD+ODD/CD represents a distinct pathological entity (Connor, Steeber, & McBurnett, 2010), as also defined in the International Classification of Diseases and Related Health Problems classification system (ICD-10, World Health Organisation, 2008). Our results appear to be more in line with the latter interpretation, although this conclusion is putative since it is not derived

from a direct comparison between ADHD groups with and without comorbidity, as the sample size of the comorbid ADHD group (i.e., *n* = 5) was not sufficient to perform these analyses. Future studies incorporating more children with ADHD with comorbid disruptive behavior disorder are warranted to shed more light on the possible mediating effects of comorbid disorders in EEG deviances in ADHD.

As for less alpha attenuation on eye opening in ADHD, this has previously been observed in another study focussing on EEG response to eye opening in children with ADHD (Fonseca et al., 2013) and has been confirmed in two studies in adults with ADHD (Loo et al., 2010; Woltering et al., 2012). The finding of less theta attenuation in ADHD following eye opening has to the best of our knowledge not been reported before. Modulation of EEG activity between eyes closed and eyes open conditions has been proposed to be an indicator of function of thalamocortical networks (Boord et al., 2008) resulting from cortical processing of visual input (Barry et al., 2007). This suggests that in the ADHD group, neuronal networks are impaired to adjust to the changes in input between eyes closed and eyes open states. Furthermore, recent studies indicate that alpha power can be regarded as a marker of arousal, since an inverse relationship has repeatedly been established between alpha power and skin conductance level (SCL) (Barry et al., 2004; Barry et al., 2009; Clarke et al., 2013), which is considered to be a reliable measure of autonomic arousal (for a review, see Critchley, 2002). For a long time, deviances in the theta frequency band have also been associated with the concept of arousal, yet recent studies failed to find an association between theta power and SCL (Barry et al., 2004, 2009). Consequently, in specific, less alpha suppression in children with ADHD may possibly be regarded as reflecting an arousal dysfunction in ADHD. Important to notice is that the ADHD group exhibited no aberrant alpha power in the conditions separately, yet expressed a difference in modulation of EEG activity between conditions. This may imply that deviances in ADHD are not characterized by a simple arousal impairment, but rather reflect a deficiency in arousal regulation. Despite the

lack of a well established autonomic measure of arousal (i.e., SCL) in our study design to strengthen this hypothesis, interpretations regarding deficient arousal modulation are in line with theoretical accounts of ADHD. According to the optimal stimulation theory, ADHD is related to a deficiency in arousal regulation with the symptomatology reflecting a behavioural strategy to compensate for a state of underarousal (Zentall & Zentall, 1983). In support of this theory, research documented that in low stimulation environments, children with ADHD showed increased stimulation seeking activity whereas in high stimulation environments, behavioural responses in children with ADHD did not differentiate from typically developing children (Antrop, Buysse, Roeyers, & Van Oost, 2005; for a review, see Zentall & Zentall, 1983). Also the state regulation account (Sergeant, 2005; van der Meere, 2005), an influential explanatory account of ADHD, which is derived from the cognitive-energetic model (Sanders, 1983), states that individuals with ADHD have difficulties in maintaining and regulating an optimal energetic arousal/activation state. Research in this respect revealed convincing behavioural and psychophysiological support for disrupted energetic state regulation in ADHD during task execution (Börger, & van der Meere, 2000; for a meta-analysis, see Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012; Sergeant, 2005; Sonuga-Barke et al., 2010; Wiersema, van der Meere, Roeyers, Van Coster, & Baeyens, 2006).

In conclusion, although no aberrant theta and TBR were found in children with ADHD in the present study, the findings refer to a consistent variation in topographic distribution in ADHD across resting state conditions compared to typically developing children, indicating the usefulness of inclusion of electrodes beyond the midline. The finding of less central alpha and theta attenuation with eye opening in children with ADHD who do not suffer from comorbid ODD/CD, suggest that EEG deviances in ADHD may reflect arousal regulation difficulties and stress the importance to take into account comorbidity with ODD/CD. Furthermore, the findings indicate that it is unlikely that

stable, univariate EEG abnormalities are implicated in all children with ADHD and that it is important to take into account state-dependent characteristics when evaluating EEG in ADHD. From a clinical perspective, this implies that cautiousness is warranted in using simple EEG measures as a supplementary diagnostic tool, as has been proposed by some researchers (Monastra, Lubar, & Linden, 2001; Snyder et al., 2008).

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CHAPTER 5

DIFFERENTIAL EFFECTS OF PINK NOISE ON THE EEG OF ADULTS WITH AND WITHOUT ADHD[1]

ABSTRACT

Objective: Previous research has shown that noise may be beneficial for cognitive performance in attention-deficit/hyperactivity disorder (ADHD). The underlying mechanisms of action of noise are however not well known. Therefore, in the current study we evaluated the impact of external auditory pink noise on electroencephalographic (EEG) activity in adults with and without ADHD. **Methods:** Three minutes eyes closed resting EEG with and without the presence of noise were compared between 40 adults with ADHD and 40 typically developing adults. The order of conditions (baseline or noise) was counterbalanced. **Results**: Alpha power attenuated in both groups with noise exposure after baseline EEG. Midline theta power also decreased from baseline to noise condition, however this was only the case for controls and was not observed in adults with ADHD. No EEG changes between conditions were detected when the noise condition preceded the condition without noise. **Conclusions:** The findings indicate that external auditory pink noise has energetic state or arousal enhancing properties. No evidence was found for a deviant brain state or underarousal during baseline resting EEG in adults with ADHD. However, adults with ADHD appear to show decreased neural adaptability in theta oscillations to noise exposure.

[1] Based on Buyck, I., & Wiersema, J.R. (2014). *Differential effects of pink noise on the electroencephalogram of adults with and without attention deficit hyperactivity disorder.* Manuscript submitted for publication.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common neurobehavioural disorder with worldwide prevalence rates varying between 5 to 7% (Willcutt, 2012). The disorder has a childhood onset and involves a persistent pattern of developmentally inappropriate inattention and/or hyperactivity and impulsivity, leading to significant impairment in daily functioning (American Psychiatric Association, 2013). Research has documented that ADHD persists throughout the lifespan in a substantial number of individuals, although the symptoms of hyperactivity and impulsivity are often less pronounced in adulthood (Faraone, Biederman, & Mick, 2006; Kooij et al., 2010; Spencer, Biederman, & Mick, 2007). Although the specific neurobiological mechanisms underlying the disorder are still unclear, converging evidence suggests disruption of the brain dopamine system to be implicated (e.g., Sagvolden, Johansen, Aase, & Russell, 2005; Volkow et al., 2007).

For a long time, the dominant view on ADHD was that it is related to deficits in executive functioning, with poor response inhibition being proposed to be the central deficit (Barkley, 1997). However a fixed core deficit in executive functioning is not universal, as not all individuals with ADHD show impaired executive functioning (for meta-analyses, see Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005 and Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005) and research has indicated that performance of individuals with ADHD is largely state and context dependent (Sergeant, 2005; Sonuga-Barke, Taylor, Sembi, & Smith, 1992; van der Meere, 2005), emphasizing the dynamic rather than the fixed nature of ADHD (Sonuga-Barke, Wiersema, van der Meere, & Roeyers, 2010).

The notion that ADHD symptoms and performance are context or state dependent is not new. In the optimal stimulation theory, Zentall and Zentall (1983) already proposed that the expression of ADHD symptoms can be interpreted as a self-

regulated compensation for a state of underarousal, thus serving as an attempt to maintain an optimal arousal level. In support of the model, research documented that in low but not in high stimulation environments, children with ADHD show increased stimulation seeking activity (Antrop, Roeyers, Van Oost, & Buysse, 2000; Antrop, Buysse, Roeyers, & Van Oost, 2002, 2005; Zentall & Zentall, 1983). The state regulation account (Sergeant, 2005; van der Meere, 2005) elaborated on the optimal stimulation theory by implementing the cognitive-energetic model of Sanders (1983), stating that individuals with ADHD have difficulties in maintaining and regulating an optimal arousal/activation state. As compensatory effort is needed to counteract a suboptimal energetic state, this may indicate impaired effort allocation in ADHD (Johnson, Wiersema, & Kuntsi, 2009). Most support for this account has come from studies that included an event rate manipulation, based on the notion that presentation rate of stimuli influences an organism's activation state (Sanders, 1983, 1998). That is, deteriorated task performance in ADHD is especially prominent in conditions that provoke suboptimal activation state by means of very fast or slow event rates, with strongest evidence of impairment in slow conditions (for a meta-analysis, see Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012), being accompanied by decreased effort allocation (Börger & van der Meere, 2000; Wiersema, van der Meere, Antrop, & Roeyers, 2006a; Wiersema, van der Meere, Roeyers, Van Coster, & Baeyens, 2006b).

Recently, a new model has been introduced into the ADHD field, which also stresses the context dependent nature of ADHD, namely the moderate brain arousal (MBA) model (Sikström & Söderlund, 2007). This model postulates that insufficient neuronal noise is generated in ADHD because of low extracellular levels of dopamine in the brain, leading to impaired dopaminergic signal transmission, which may explain worse performance in ADHD in certain conditions. In the MBA model it is predicted that presenting external environmental auditory random interference (white or pink noise, generally called "noise") in ADHD can modulate neuronal noise and accordingly restore

neural activity and normalize performance (Sikström & Söderlund, 2007). These effects are accounted for by stochastic resonance, a mechanism whereby weak signals in the brain are amplified by adding environmental noise, hence passing the threshold for signal transmission in the neurotransmitter system and improving cognitive performance. The stochastic resonance curve follows an inverted U-shape, indicating that only an optimal amount of added external noise results in the maximum output (for a review, see Moss, Ward, & Sannita, 2004; McDonnell, & Abbot, 2009). Consequently, neurocomputational simulations in the MBA model show that more noise is needed to achieve stochastic resonance and hence higher cognitive performance in hypodopaminergic systems compared with normal functioning dopamine systems (Sikström & Söderlund, 2007). So far, a few studies have denoted the beneficial impact of noise on cognitive performance in ADHD and related symptomatology. In specific, memory performance of children with ADHD was found to improve during administration of external auditory white noise, whereas performance in typically developing children deteriorated (Söderlund, Sikström, & Smart, 2007). Moreover, in a non-clinical group, differential effects of white noise on performance were observed in accordance with attentional abilities of the participants. That is, while adding noise was detrimental for memory performance in attentive children, performance of inattentive children was enhanced and episodic memory discrepancies between attentive and inattentive children disappeared (Söderlund, Sikstrom, Loftesnes, & Sonuga-Barke, 2010).

Despite these promising results and potentially important clinical implications, knowledge about the underlying neurobiological mechanisms of action is limited, which calls for further research (Söderlund et al., 2007). In other words, the mentioned studies seem to be supportive of the beneficial effect of noise in individuals with low attentional abilities or ADHD, but they do not give insight into why noise was beneficial for performance. As Söderlund and colleagues (2010) argue themselves, another

theoretical interpretation of the data would be that noise in a general way increases arousal, making participants more alert. In order to provide more insight into the underlying mechanism of noise effects in ADHD, studies are needed that include measures that exceed the behavioural level. Therefore in the current study, we will evaluate the impact of external noise on resting electroencephalogram (EEG) in typically developing individuals and individuals with ADHD. EEG activity reflects the summation of the synchronous activity of many neurons and consists of oscillations at a variety of frequencies, which relate to different brain states (Loo & Makeig, 2012).

A large body of literature has established enhanced theta power and increased theta/beta ratio (TBR) in ADHD, but also deviant alpha power has been reported (for reviews, see Barry, Clarke, & Johnstone, 2003 and Barry & Clarke, 2009). Interestingly, these EEG deviances in ADHD have often been interpreted as reflecting altered cortical state (e.g., Mann, Lubar, Zimmerman, Miller, & Muenchen, 1992; Monastra et al., 1999; van Dongen-Boomsma et al., 2010). While higher theta or TBR in ADHD has long been argued to indicate underarousal (e.g., Lubar, 1991; Mann et al., 1992), more recent work could not validate this, as theta and TBR were not found to be correlated with skin conductance level (Barry et al., 2004; Barry, Clarke, Johnstone, McCarthy, & Selikowitz, 2009; Dupuy, Clarke, Barry, Selikowitz, & McCarthy, 2014), a well-known indicator of autonomic arousal (Critchley, 2002), which led to a reinterpretation of TBR as indexing "activation" (Barry et al., 2009). Instead, alpha power was found to be inversely related to skin conductance level and seems therefore closely related to arousal (Barry et al., 2004, 2009; Dupuy et al., 2014). Evaluating EEG with noise exposure may thus not only enhance insights in the underlying working mechanisms of noise but may also add to the understanding of the significance of EEG deviances in ADHD.

In the present study, for the first time, resting EEG will be evaluated in conditions without and with the administration of pink noise in adults with ADHD and typically developing individuals. Although findings regarding deviant theta or TBR in ADHD are

not fully consistent across studies, if deviant theta power and TBR are reliable markers for ADHD, the ADHD group is expected to show enhanced theta power and TBR in the baseline resting condition. If noise normalizes neural functioning in ADHD, a normalized EEG pattern is expected in the noise condition. If noise merely acts through generally increasing arousal, alpha power is expected to decrease in the presence of noise. Interactions between diagnostic status and type of resting condition might appear for alpha, as EEG studies on eyes opening have documented abnormal alpha reactivity in ADHD (Fonseca, Tedrus, Bianchini, & Silva, 2013; van Dongen-Boomsma et al., 2010; Woltering, Jung, Liu, & Tannock, 2012).

METHOD

Participants

40 adults with ADHD and 40 typically developing adults between the ages of 18 and 55 years participated in the study (Table 1). Groups did not differ in age ($F(1, 79) < 0.01$, $p = .94$), IQ ($F(1, 79) = 0.89$, $p = .35$) and sex. Both adults with and without ADHD were recruited through advertisements in local magazines and acquaintances of the researchers. Furthermore, the ADHD group consisted of adults who previously participated in an experiment and adults who attended ADHD self support groups. Individuals with ADHD were required to meet DSM-IV criteria for the diagnosis of ADHD across the entire lifespan, ascertained by a semi-structured clinical interview (Diagnostisch Interview voor ADHD bij Volwassenen (DIVA 2.0), Kooij & Francken, 2010). The presence of childhood ADHD was furthermore retrospectively assessed with a translated version of the 61-item Wender Utah Rating Scale (WURS) (Ward, Wender, & Reimherr, 1993), whereas ADHD manifestation through the life course was evaluated with a translated version of the 46-item DSM-IV ADHD rating scale (Du Paul, Power, Anastopoulos, & Reid, 1998). Following published diagnostic guidelines, thresholds

were set at four symptoms in either the inattentive or the hyperactive/impulsive domain to meet criteria for ADHD during adulthood (Kooij et al., 2010). Since a longer wash-out period is required for non-stimulants, participation of adults using medication to reduce ADHD symptomatology in daily life was restricted to individuals taking stimulants. To control for medication effects, adults with ADHD using stimulants were asked to refrain from medication 48 hours before participating in the experiment.

Table 1. Sample characteristics

	CONTROL (*n* = 40)	ADHD (*n* = 40)
Male/female	20/20	20/20
Age in years	*M* 31.98 (*SD* 10.99)	*M* 31.80 (*SD* 10.30)
Estimated FSIQ	*M* 111.15 (*SD* 10.16)	*M* 108.80 (*SD* 12.08)
ADHD RS-IV inattention	*M* 5.83 (*SD* 4.16)	*M* 20.93 (*SD* 6.28)
ADHD RS-IV hyperactivity impulsivity	*M* 7.13 (*SD* 4.03)	*M* 19.08 (*SD* 7.14)
ADHD subtype I/C		16/24
Number of segments rest	*M* 144.88 (*SD* 31.09)	*M* 138.28 (*SD* 32.95)
Number of segments noise	*M* 144.05 (*SD* 34.79)	*M* 129.05 (*SD* 33.30)

Note. M: mean, SD: standard deviation, FSIQ: Full Scale Intelligence Quotient, ADHD RS-IV: ADHD Rating Scale-IV, I: inattentive subtype, C: combined subtype

Exclusion criteria for all participants were history of brain related illness, neurological disorder and estimated IQ below 80. Intelligence functioning was evaluated by an abbreviated Wechsler Adult Intelligence Scale-III (WAIS-III) (Ryan & Ward, 1999). For one adult with ADHD, estimation of IQ was obtained through only 4 subtests of the WAIS since we were not able to reach the person to complete the test administration. The Adult Self Report (Achenbach & Rescorla, 2003) was administered to screen for possible psychiatric disorders in the control group. Adults reaching clinical scores on the ASR and scores above cut off for ADHD diagnosis on adult ADHD ratings were excluded from the control group.

Procedure

The research protocol was approved by the ethic committee of the Faculty of Psychology and Educational Sciences at Ghent University. Following the explication of procedures, participants signed an informed consent. Subjects were asked to sit down in front of a monitor and were then fitted with the electrophysiological equipment. During the study, the experimenter was present in the room but sat out of sight of the participants. After the participants were instructed to close their eyes, two resting EEGs varying in noise level (with and without presentation of pink noise) were recorded for three minutes in a counterbalanced order (see also Söderlund et al., 2007, 2010) across participants. Pink noise was used, because white noise can be perceived as aversive due to much power in the high frequencies. Pink noise, also referred to as 1/f noise, is a random signal whose power spectral density decreases as its frequency increases. Noise was presented with a sound level of 80 dB via two external loudspeakers, placed on the left and right side of a computer screen. Subsequently, several tasks were administered, followed by another resting EEG session. In the current paper, the focus is on the resting EEG conditions with and without exposure of noise before task execution.

Electrophysiological procedure

EEG data were obtained with an electrode cap employing 128 active 10 mm Ag/AgCl electrodes placed according to the 10-5 International System (Oostenveld & Praamstra, 2001) and amplified with a QuickAmp amplifier (Brain Products). The ground electrode was enclosed within the cap at Fpz and an average reference derivation was used. Signals were monitored using Brain Vision Recorder software (version 1.10) with a sample rate of 500 Hz and a low pass filter of 50 Hz. Vertical eye movement was recorded by an electrode enclosed in the cap above the right eye (Fp2) and an electrode placed in line with the pupil below the right eye, whereas horizontal eye movement was recorded from electrodes enclosed in the cap next to the eyes (F9 and F10).

Analyses of EEG data were performed using Brain Vision Analyzer software (version 2.0.1). EEG data were filtered with a high pass filter of 0.5 Hz, a low pass filter of 50 Hz and a notch filter of 50 Hz. Data were segmented in 2 s epochs with 1 s overlap. Eye movement correction was conducted according to the Gratton and Coles algorithm (Gratton, Coles, & Donchin, 1983). Segments were rejected from further analyses if absolute difference of amplitudes exceeded 120 µV. The remaining number of segments for analyses did not differ between conditions ($F(1, 78) = 3.56$, $p = .06$) and groups ($F(1, 78) = 2.45$, $p = .12$) (Table 1). Subsequently, spectral power was calculated using Fast Fourier Transform and the transformed data were averaged. EEG measures derived from 21 electrodes were averaged in 9 regions for further analysis: left frontal (AF3, F3, F7), midline frontal (AFz, Fz), right frontal (AF4, F4, F8), left central (T7, C3), midline central (Cz), right central (T8, C4), left posterior (P7, P3, O1), midline posterior (Pz, Oz), and right posterior (P8, P4, O2) (see Clarke et al., 2011). Absolute power estimates were derived for theta (4-7.5 Hz) and alpha (7.5-12.5 Hz) frequencies. TBR was calculated by dividing power in the theta band by power in the beta band. A natural logarithmic (ln) transform was used to approach normal spreading of the data.

Statistical analyses

EEG activity with and without presentation of noise in the ADHD and control group were compared by separate analyses of variance (ANOVAs) with repeated measures for theta and alpha power and for TBR. Condition (recording without noise versus recording with noise), sagittal region (frontal, central, posterior) and lateral region (left, midline, right) were within-subject factors and group (ADHD, non-ADHD) and condition order (first EEG recording with noise versus first EEG recording without noise) were between-subject factors. Condition order was entered as a between subject factor to evaluate whether results are affected by the sequence of conditions. We were especially interested in (interaction with) group and (interaction with) condition effects.

RESULTS

The topographic power distributions for eyes closed resting conditions with and without noise exposure and the differences in power distribution between conditions in each frequency band and TBR are presented in Figure 1.

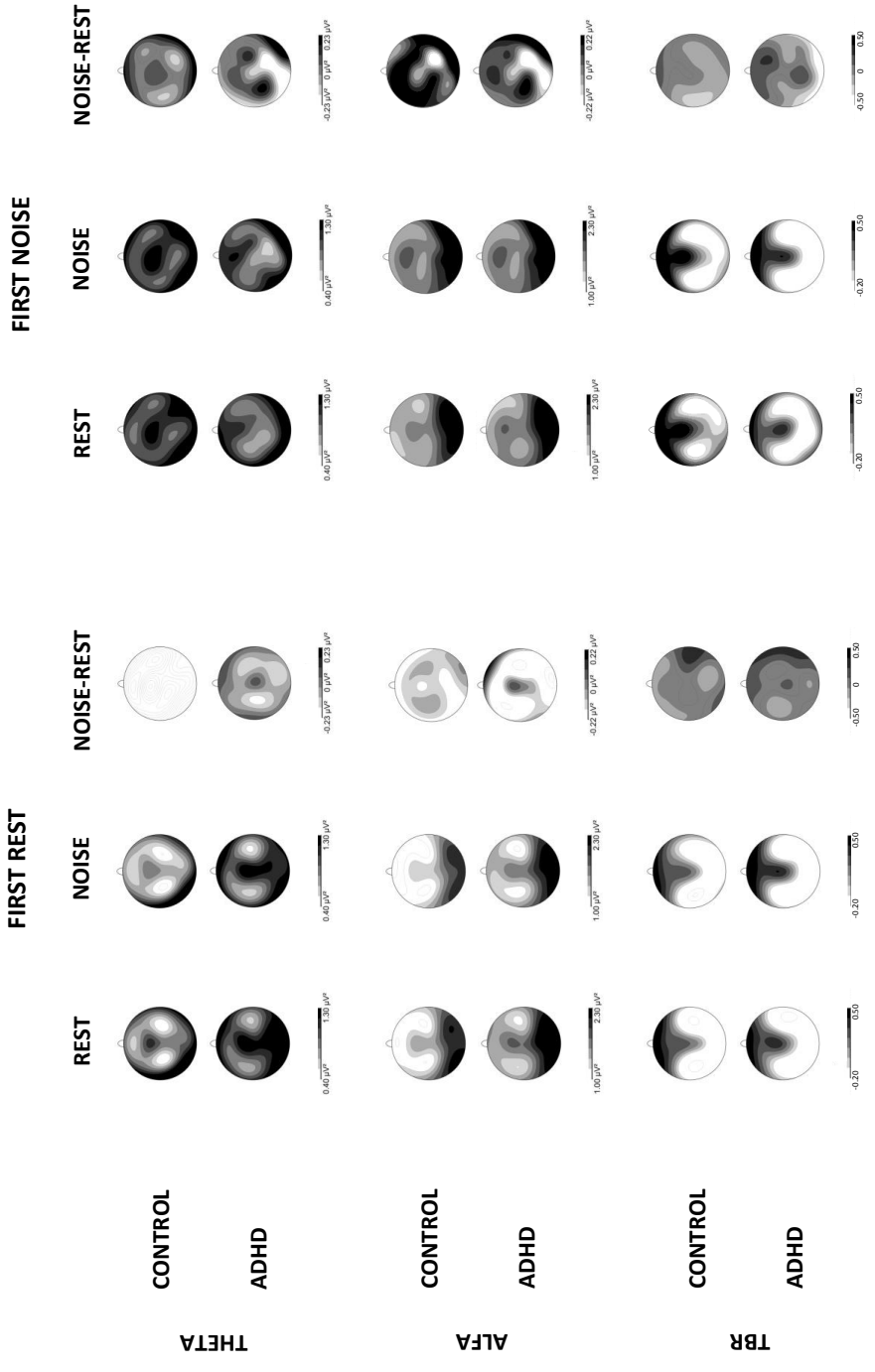

Figure 1. Spectral analysis for rest and noise conditions. Absolute power for theta and alpha frequency bands ($ln\mu V^2$) and TBR (theta/beta ratio) (ln). Differences between rest and noise conditions.

Theta power

A significant condition effect was found for theta activity ($F(1, 76) = 6.38$, $p = .01$, $\eta^2_p = .08$), indicating lower power in the resting condition with noise than without noise. However, as indicated by the interaction effect between condition and condition order ($F(1, 76) = 10.99$, $p = .001$, $\eta^2_p = .13$), this effect only appeared when the baseline resting condition without noise was presented first ($F(1, 38) = 14.92$, $p < .001$, $\eta^2_p = .28$). Furthermore, a significant interaction appeared between condition, group, lateral region and condition order ($F(1.70, 129.05) = 6.05$, $p < .01$, $\eta^2_p = .07$). Further testing revealed that when the noise condition was presented after the baseline EEG condition, midline theta power in the control group attenuated ($F(1, 38) = 19.99$, $p < .001$, $\eta^2_p = .51$) while this was not observed in the ADHD group ($F(1, 38) = 0.37$, $p = .55$, $\eta^2_p = .02$). This resulted in a higher theta power in adults with ADHD than in typically developing adults in the presence of noise after recording a baseline resting condition ($F(1, 38) = 5.40$, $p = .03$, $\eta^2_p = .12$) (Figure 2).

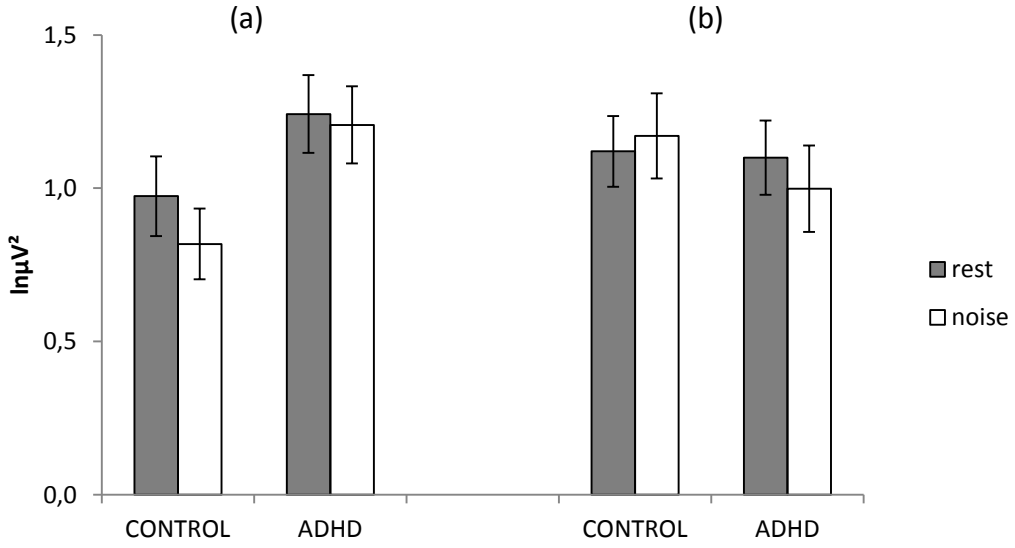

Figure 2. Mean theta power across midline electrodes for adults with ADHD and controls in (a) first rest and (b) first noise condition. Error bars represent the standard error of the mean.

Alpha power

A significant interaction between condition and condition order was found for alpha power ($F(1, 76) = 14.53$, $p < .001$, $\eta^2_p = .16$) (Figure 3), reflecting a power reduction with noise when noise followed the baseline measurement ($F(1, 38) = 22.18$, $p < .001$, $\eta^2_p = .37$) but not when the noise condition was presented first ($F(1, 38) = 1.46$, $p = .24$, $\eta^2_p = .04$). In addition, a trend for an interaction between group, condition, condition order and lateral region was detected ($F(1.33, 101.37) = 2.65$, $p < .10$, $\eta^2_p = .03$). However, no significant results were obtained with post hoc analyses to explain this effect.

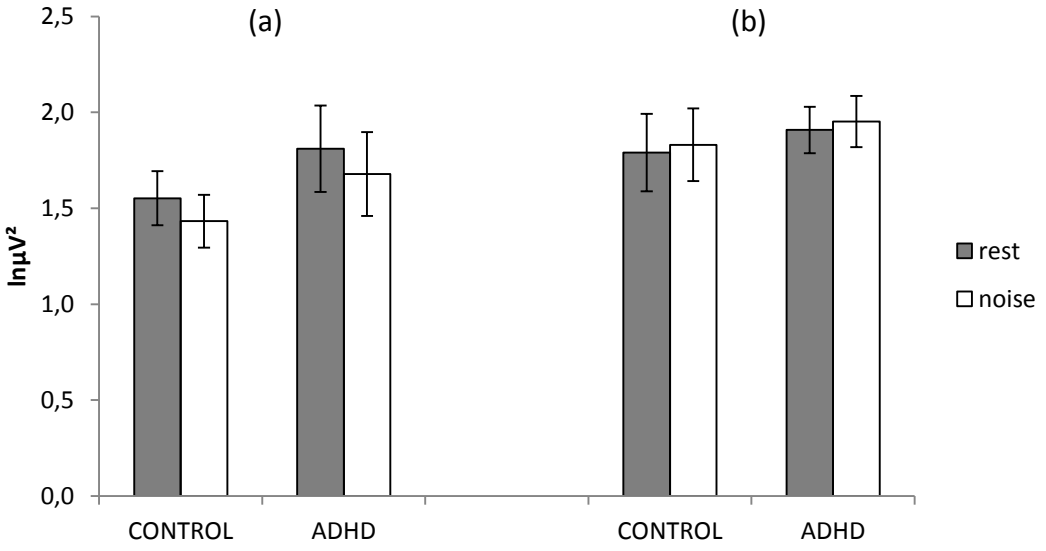

Figure 3. Mean alpha power across the scalp for adults with ADHD and controls in (a) first rest and (b) first noise condition. Error bars represent the standard error of the mean.

TBR

For TBR, a significant interaction emerged between group, condition, lateral region and condition order ($F(2, 152) = 3.67$, $p = .03$, $\eta^2_p = .05$). Post hoc analyses to further explore this effect, revealed no significant results.

DISCUSSION

This is the first study that investigated the impact of noise on resting EEG activity in an ADHD population. While studies have denoted a beneficial effect of noise on cognitive performance in ADHD, little is known about the underlying working mechanisms of noise on a brain functioning level. The MBA model explains the beneficial effects of noise on ADHD by the restoration of impaired dopamine transmission, resulting from the mechanism of stochastic resonance (Sikström & Söderlund, 2007). Alternatively, a general arousal enhancing effect might explain the effects, as ADHD has often been considered to be related to deviances in energetic arousal state (Sonuga-Barke et al., 2010).

Groups did not differ in theta, TBR, or alpha across conditions, except for higher midline theta power in adults with ADHD when noise was presented after baseline resting EEG, due to absent attenuation of theta in the ADHD group with noise. The comparable alpha power between groups is not fully unexpected, since inconsistent findings in this frequency band have been reported across resting EEG studies (Bresnahan & Barry, 2002; Bresnahan, Barry, Clarke, & Johnstone, 2006; Hermens et al., 2004; Koehler et al., 2009; Liechti et al., 2013; Loo et al., 2009; van Dongen-Boomsma et al., 2010; Woltering et al., 2012) and suggest that arousal was not decreased in adults with ADHD. As for theta power and TBR, many studies have documented these parameters to be elevated in ADHD (for reviews, see Barry et al., 2003 and Barry & Clarke, 2009), however our findings are in accord with more recent studies that also

could not replicate enhanced theta or TBR in adult ADHD (Liechti et al., 2013; Loo et al., 2013; Poil et al., 2014; van Dongen-Boomsma et al., 2010).

As for the effects of noise on the EEG parameters, both groups showed a significant reduction of alpha power with noise exposure after recording a baseline resting EEG, while midline theta power only reduced in the control group and TBR was not found to modulate with noise. Research addressing the effects of noise on brain wave activity is scarce, limited to healthy controls and so far did not examine theta power and TBR. Yet, our findings regarding alpha attenuation with noise exposure after a baseline EEG are in line with other studies (Cho, Hwang, & Choi, 2011; Davies, 1968; Mohammad, Saidatul, & Tamjis, 2009), indicating a general arousal enhancing effect of pink noise. Reduction in alpha power has also been noticed in studies addressing other manipulations of arousal, such as opening of the eyes (e.g., Barry, Clarke, Johnstone, Magee, & Rushby, 2007; Boytsova & Danko, 2010) or administration of caffeine (e.g., Barry, Clarke, & Johnstone, 2011; Siepmann & Kierch, 2002). As mentioned in the introduction, theta differs from alpha in that it does not seem to be directly related to autonomic arousal as it was not found to be correlated with skin conductance level (Dupuy et al., 2014), however enhanced theta is considered as a well-known EEG signature for fatigue or drowsiness (e.g., Barwick, Arnett, & Slobounov, 2012; Jödicke et al., 2013; Lal & Craig, 2001; Oken, Salinsky, & Elsas, 2006) and as with alpha several studies have reported a reduction in theta with eye opening (e.g., Barry et al., 2007, 2009; Boytsova & Danko, 2010) or caffeine intake (Gilbert, Dibb, Plath, & Hiyane, 2000). All together, this seems to support the notion that exposure to auditory external pink noise enhances arousal or energetic state.

According to the MBA model, noise has the potential to induce beneficial effects in ADHD by means of stochastic resonance through modulating properties of dopamine-related gain and neural noise in determining neural responsivity (Sikström & Söderlund, 2007). Do the current findings provide support for the MBA model? First, the MBA

model suggests that individuals with ADHD or low attentive individuals in general have a low gain parameter owing to low levels of baseline dopamine neuron firing. However, as mentioned, no EEG differences were observed between groups during the baseline EEG recording, providing no support for a deviant brain state in ADHD. Moreover, adding noise decreased theta power in controls, but not in adults with ADHD, resulting in higher midline theta power in ADHD when noise was presented. From an MBA model perspective, this might indicate that the level of noise presented in the current study was not sufficient to obtain the same effects on theta power in the ADHD group compared to the control group. That is, according to the predictions of the model, more noise may be needed to achieve stochastic resonance in dopamine deprived systems and hence neural responsivity (Sikström & Söderlund, 2007; Söderlund et al., 2010). However, the finding that none of the EEG measures, including theta power, could distinguish the groups during baseline measurement argues against this explanation. In addition, a similar noise level was used (80 dB) to that in studies where noise was found to be effective on performance (Söderlund et al., 2007, 2010). Moreover, the adults with ADHD included in the current study had significantly higher inattention symptoms than the controls. Nevertheless, further research could elaborate on this by including different levels of noise in the study design in order to investigate potential differential effects related to noise level in ADHD. Perhaps, investigating EEG during conditions where individuals with ADHD show normalized performance will provide more insight into the underlying mechanism of the earlier observed beneficial effect of noise in ADHD. Although the current study does not allow to fully test the MBA model as no neurochemical responses to noise were evaluated, recently, Pålsson and colleagues (2011) studied the effect of noise on the startle response in a rat model of ADHD and showed that both control and ADHD strains (i.e., spontaneous hyperactive rats) benefited from noise, but the noise effects were also found in rats with dopamine

lesion, indicating that noise effects do not necessarily act through dopamine-related gain (Pålsson, Söderlund, Klamer, & Bergquist, 2011).

The finding of different modulation of EEG activity with noise in ADHD may suggest a deficiency in brain state regulation or adaptation rather than the presence of a fixed state of underarousal, which would generally be in line with the state regulation account of ADHD, implying impaired regulation of arousal/activation levels (Sergeant, 2005; Sonuga-Barke et al., 2010; van der Meere, 2005). The state regulation account however relates ADHD to impaired top-down modulation of arousal systems, i.e. difficulty with allocating extra effort in order to counteract suboptimal energetic state (Börger & van der Meere, 2000; Wiersema et al., 2006a,b), while noise has been argued to act through bottom-up modulation of arousal systems (Sanders, 1983). Hence, the current finding may extend the state regulation account, by suggesting that bottom-up regulation of energetic state in ADHD is deviant as well. Although we are aware that this may seem a premature conclusion and more research is needed to further test this hypothesis, some additional support for this proposition may be found in EEG studies on ADHD addressing resting conditions that differ in arousal level (i.e., eyes open versus eyes closed), in which also altered responsivity of theta in ADHD was noticed to opening of the eyes (Buyck & Wiersema, submitted; Liechti et al., 2013), suggesting deficiencies in adaptability in theta power in ADHD. This may also possibly partly explain some inconsistent findings regarding deviating theta power in ADHD across studies, since this implies plausible divergence in theta power in individuals with ADHD depending on contextual/state features. Although speculative, the current findings may possibly also clarify some effects of neurofeedback treatment in ADHD, in which traditionally theta power is learned to be modulated to improve ADHD symptomatology. Perhaps beneficial effects of this training can be related to acquiring a greater adaptability in theta power rather than fixing a static deficit (i.e., higher theta or TBR (Barry & Clarke,

2009)). However, future studies are warranted to confirm the robustness and validity of our results and to elaborate on this hypothesis.

The fact that EEG power did not change between conditions when noise was presented first, may be the result from an after effect of noise on the following resting condition. In animal research, it is well-established that arousal upon brief sensory stimuli generally lasts for a while in order to facilitate goal-directed behaviour that promotes survival and well-being (for reviews, see Jing, Gillette, & Weiss, 2009 and Pfaff, Martin, & Faber, 2012). As an after effect of internal noise has repeatedly been demonstrated on sensory nerves in humans (Chiou-Tan et al., 1996, 1997; Chuang et al., 1999; Chuang & Chiou-Tan, 2000; Tran, Moss, Robinson, & Chiou-Tan, 2000), the question can be raised whether similar mechanisms may act on brain oscillations. However, our study design is not feasible to verify this hypothesis, since this requires registration of baseline resting EEG before recording EEG with noise, followed by another EEG registration without noise for all participants. Also, it should be taken into account that the participants in the different condition orders may have experienced a different level of arousal prior to the exposure to noise as sitting quietly for three minutes in a silent room may elicit a different (i.e., lower) basic arousal level (baseline first) than getting fitted with the test material (noise first). However, the experimental design does not enable a within-subjects comparison of the condition orders, and a between-subjects comparison of condition orders is hampered because spectral parameters are known to express a considerable inter-individual variability (Poil et al., 2014; van Dongen-Boomsma et al., 2010). Further research addressing order effects of noise is imperative to elaborate on the impact of noise on resting EEG, since this may have potentially important implications for the possible use of noise for clinical purposes.

Since research already demonstrated associations between measures of central and autonomous nervous system functioning (Olbrich et al., 2011), incorporating for

instance electrodermal measures, that have been shown to be a reliable marker of arousal (for a review, see Critchley, 2002), could provide more insights into the relation between the concept of arousal and the effect of noise presentation in ADHD.

To conclude, this first study on the effects of noise on brain wave activity in an ADHD population revealed some interesting findings on the nature of EEG discrepancies in ADHD and the significance of noise on brain functioning in adults with as well as without ADHD. First, the current findings seem to validate that noise exposure may serve as an energetic state or arousal enhancing procedure. Second, although our results did not confirm discrepancies in alpha power nor in theta or TBR in adults with ADHD compared to typically developing adults, some evidence was found for dynamic, state dependent deficiencies in theta power in ADHD. That is, while midline theta activity attenuated in typically developing adults with noise after recording of baseline EEG, this was not observed in the ADHD group. This may reflect aberrant adaptability in this frequency band in adults with ADHD.

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CHAPTER 6

TASK-RELATED EEG DEVIANCES IN ADULTS WITH ADHD[1]

ABSTRACT

Objective: The aim of this study was to provide more insights into the functional significance of EEG deviances in ADHD by evaluating quantitative EEG during performance on a task loading on activation level and a task tapping top-down executive control. **Methods**: Behavioural performance and EEG were compared between 24 adults with ADHD and 20 typically developing adults during execution of a simple slow paced 2-choice reaction time (2-CRT) task and a regular paced flanker task. **Results**: During the slow 2-CRT task, adults with ADHD responded slower, more variably, and tended to make more errors of commission. Although being slower, adults with ADHD showed equally large congruency effects during flanker task performance, indicating intact interference inhibition. In the slow 2-CRT task, (midline) theta and beta power were higher in the ADHD group than in the control group, whereas no significant EEG group differences were observed in the flanker task. A moderate positive correlation between theta power and errors of commission was found in the 2-CRT task for adults with ADHD. **Conclusions**: Adults with ADHD performed worse on a task inducing a low activation level but showed intact interference inhibition. The EEG findings are in accord with this, showing abnormal EEG patterns in ADHD only when activation level was taxed, not when top-down executive control was required. Time-on-task effects could not explain deviances between groups. The findings indicate that EEG deviances in ADHD are task dependent and may be related to a suboptimal energetic state, rather than impaired top-down executive control.

[1] Based on Buyck, I., & Wiersema, J.R. (2014). *Task-related electroencephalographic deviances in adults with attention deficit hyperactivity disorder.* Manuscript submitted for publication.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with a childhood onset, affecting approximately 5 to 7 % of the worldwide population (Willcut, 2012). The disorder comprises a pattern of developmentally inappropriate symptoms of inattention and/or hyperactivity and impulsivity, resulting in significant impairments in social, academic or occupational functioning (American Psychiatric Association, 2013). ADHD-related symptomatology has been documented to persist throughout the lifespan in about two thirds of individuals, although often with a more subtle expression of symptoms of hyperactivity and impulsivity in adulthood (Faraone, Biederman, & Mick, 2006; Kooij et al., 2010; Spencer, Biederman, & Mick, 2007).

While its etiology is not fully understood, over the past decades the neural correlates of ADHD have been widely investigated by means of electroencephalography (EEG) (Loo & Makeig, 2012). Most EEG studies in ADHD have evaluated brain wave activity during resting conditions with either eyes closed or eyes open, often revealing an elevated theta activity and/or an enhanced theta/beta ratio (TBR) in ADHD across the lifespan (Barry, Clarke, & Johnstone, 2003, for a review; Buyck & Wiersema, 2014; Clarke, Barry, McCarthy, Selikowitz, & Johnstone, 2007; Clarke et al., 2011; Dupuy, Clarke, Barry, McCarthy, & Selikowitz, 2011; Dupuy, Barry, Clarke, McCarthy, & Selikowitz, 2013; González-Castro, Rodríguez, López, Cueli, & Álvarez, 2013; Hermens et al., 2004; Koehler et al., 2009; Lansbergen, van Dongen-Boomsma, Spronk, & Buitelaar, 2011; Loo et al., 2010; Shi et al., 2012; Woltering, Jung, Liu, & Tannock, 2012). Yet, lately the consistency of these deviances characterizing the EEG profile of the total ADHD group is debated, since some studies could not invariably replicate these findings (Buyck & Wiersema, submitted; Coolidge, Starkey, & Cahill, 2007; Liechti et al., 2013; Loo et al., 2009, 2013; Nazari, Wallois, Aarabi, & Berquin, 2011; Ogrim, Kropotov, & Hestad, 2012;

Poil et al., 2014; Swartwood, Swartwood, Lubar, & Timmermann, 2003; van Dongen-Boomsma et al., 2010).

Less often, quantitative EEG in ADHD has been studied during task performance. As different tasks may tap diverse cognitive(-energetic) processes, which are not easily discerned during resting state conditions, applying this approach may increase the understanding of EEG deviations in ADHD. Most studies regarding task-related EEG activity in ADHD are conducted in children. Some of these report similar theta or TBR deviances as observed in resting conditions during a variety of tasks (El-Sayed, Larsson, Persson, & Rydelius, 2002; Janzen, Graap, Stephanson, Marshall, & Fitzsimmons, 1995; Mann, Lubar, Zimmerman, Miller, & Muenchen, 1992; Monastra et al., 1999; Monastra, Lubar, & Linden, 2001), however other studies could not confirm these findings (Nazari et al., 2011; Swartwood et al., 2003). Fewer studies have addressed task-related EEG activity in adult ADHD, also documenting inconsistent results. That is, Monastra and colleagues (1999) reported that adults with ADHD showed increased TBR during performance on several tasks. Yet, in another study, theta and TBR were found to be normal in adults with ADHD during a Wisconsin Card Sorting Test, a Paced Auditory Serial Addition Test, and a Continuous Performance Test (CPT), while alpha activity was elevated during the CPT (White, Hutchens, & Lubar, 2005). In contrast, alpha attenuation has also been reported in adults with ADHD while performing the CPT (Loo et al., 2009). Interestingly, some studies also refer to time-on-task effects in differences between groups during the CPT. In specific, one study found reduced frontal beta power in ADHD in the second part of a visual CPT, while beta was not divergent during the first part, and a similar observation was made for theta power, being enhanced in ADHD only at the end of the task in an auditory CPT (Rasey, Craig, & Lubar, 1999). Another study observed an alpha increase with time-on-task in the control group but not in the ADHD group (Loo et al., 2009). Although not concordant, these results nevertheless suggest

that it may be important to take into account time-on-task effects when investigating task-related EEG activity in ADHD.

While aberrant theta and TBR have frequently been reported in ADHD, the significance of these deviances is still not fully understood. Concerning this, evaluating quantitative EEG during task performance may be helpful, because one can include experimental manipulations that enable to test existing hypotheses. In this respect, one of the most influential explanations regarding enhanced theta and TBR is that they represent cortical hypoarousal (e.g., Mann et al., 1992; Monastra et al., 1999). However, this account has been challenged since recent studies failed to find an association between a well established autonomic measure of arousal (i.e., skin conductance level) and theta or TBR (Barry, Clarke, Johnstone, McCarthy, & Selikowitz, 2009; Clarke et al., 2013). These findings led to a reframing of TBR in terms of impaired functionality of cortical activation (Barry et al., 2009). Noteworthy, the concepts of arousal and activation (although perhaps conceptually not completely overlapping due to evolving from different areas of research) are also key concepts of the state regulation account, which is a prominent neuropsychological model of ADHD (Sergeant, 2000; van der Meere, 2005). This account is based on the cognitive-energetic model of Sanders (1983, 1998) and states that impairments in ADHD result from a deficiency in maintaining and regulating an optimal energetic state in challenging suboptimal situations (Sonuga-Barke, Wiersema, van der Meere, & Roeyers 2010). Important to note is that the cognitive-energetic model, together with other influential accounts, abandons the uni-dimensional concept of arousal, postulating an effortful top-down mechanism (compensatory effort) needed to counteract performance decrements due to suboptimal arousal or activation levels (Hockey, 1997; Mulder, 1986; Pribram & McGuinness, 1975; Sanders, 1983, 1998). Within the cognitive-energetic framework, 'arousal' is quantified as the phasic physiological response to stimulus processing, whereas 'activation' is defined as a tonic vigilant physiological readiness for action

(Pribram & McGuinness, 1975; Sonuga-Barke et al., 2010). In order to avoid confusion, the current study will use 'activation' as conceptualized by the state regulation account (Sonuga-Barke et al., 2010). According to the cognitive-energetic model of Sanders (1983), a slow presentation rate of stimuli induces a state of underactivation. Indeed, numerous studies addressing a large variety of tasks have demonstrated that individuals with ADHD perform worse when stimuli are presented at a slow pace (e.g., 8 s), but normal when presented at a moderate pace (e.g., Brown & Vickers, 2004; Leung, Leung, & Tang, 2000; Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012 for a meta-analysis; Rubia, Taylor, Taylor, & Sergeant, 1999; Scheres, Oosterlaan, & Sergeant, 2001; Wiersema, van der Meere, Antrop, & Roeyers, 2006a; Wiersema,van der Meere, Roeyers, Van Coster, & Baeyens, 2006b). Hence, investigating EEG activity during a task with a slow event rate might be a valuable approach to provide us with information about the potential relationship between enhanced theta or TBR in ADHD and a suboptimal activation state.

Alternatively, increased slow to fast wave ratios have been explained as reflecting reduced cortical control over subcortical structures (Schutter, Leitner, Kenemans, & van Honk, 2006; Knyazev, 2007), as slow waves are suggested to arise from subcortical structures, while fast waves originate from thalamo-cortical and cortico-cortical circuits (Schutter & Knyazev, 2012). It is then assumed that a balance to slow EEG frequencies (e.g., theta) results in response activation, while a balance to fast frequencies (e.g., beta) generates inhibition (Schutter et al., 2006). Interestingly, again this parallels a well-known explanatory model of ADHD, namely the executive dysfunction theory of ADHD, which postulates impairments in executive functioning (i.e., top down executive control), particularly in response inhibition, to be the core problem of ADHD (Barkley, 1997). Indeed, ADHD has frequently been related to executive dysfunction, including response inhibition (for meta-analyses, see Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005 and Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005),

although it has been stressed that executive dysfunction is neither necessary nor sufficient to cause all cases of ADHD (Willcutt et al., 2005). Evaluating EEG activity in ADHD during a task that taps top-down executive control may be helpful in gaining more insights into the possible association between aberrant theta or TBR in ADHD and impairment in executive functioning.

So far, the literature regarding task-related EEG activity in adulthood ADHD is scarce and research rarely used a theory-driven approach with respect to selection of tasks. Therefore, in the current study we chose our tasks to test two existing hypotheses (reduced activation; decreased executive top-down control) that relate to well-known explanatory accounts of ADHD (state regulation account; executive dysfunction theory), which may help to gain further insights in the significance of aberrant EEG activity in ADHD. In specific, EEG will be evaluated during execution of a slow paced 2 choice reaction time (2-CRT) task and a flanker task. The 2-CRT task has a very slow event rate (8 s inter stimulus interval), which induces a low activation state during task execution (Metin et al., 2012; van der Meere, 2005). Little executive or inhibitory control is required as only a simple decision has to be made (press left or right), when a letter appears on the screen, indicating the required response (Hogan, Vargha-Khadem, Kirkham, & Baldeweg, 2005; Bitsakou, Psychogiou, Thompson, & Sonuga-Barke, 2008). In contrast, in the flanker task stimuli are presented at a moderate pace to induce moderate levels of activation, but the task loads high on top-down executive control. The difference between RT and error rate on incongruent trials (target arrow flanked by arrows pointing in the opposite direction) and congruent trials (target arrow flanked by arrows pointing in the same direction) reflects interference inhibition and a larger score indicates less top-down executive control. Since previous research has indicated divergent time-on-task effects on EEG in ADHD (Loo et al., 2009; Rasey et al., 1999), which may hamper correct interpretation of results when not taken

into account, analyses will comprise a first, middle and third part of each task. Finally, links between EEG indices and performance will be examined by means of correlations.

From a state regulation account perspective, impaired performance on the slow 2-CRT task is expected in the ADHD group, reflected in increased reaction time (RT), variability of RT, and/or accuracy, due to underactivation. From a disinhibition perspective, larger congruency effects are expected in adults with ADHD in the flanker task, indicating worse interference inhibition. If theta power and TBR are related to activation deficits in ADHD, they are expected to deviate in the 2-CRT task. If aberrant theta and TBR are associated with impaired top-down executive control, deviance between groups is expected in the flanker task. The paucity and inconsistency of data in the literature hampers formulating strong hypotheses regarding the associations between EEG parameters and task performance measures, although existent literature suggests a difference in association patterns between groups (Loo et al., 2009).

METHOD

Participants

Participants were twenty-four adults with ADHD and twenty control adults, aged 18 to 55 years, who were recruited through staff members and local advertisements. Furthermore, the ADHD group comprised former participants of an experiment and adults who attended ADHD self support groups. Before participation, adults with ADHD had received a diagnosis in a clinical setting. ADHD diagnosis was ascertained by a semi-structured clinical interview (Diagnostisch Interview Voor ADHD bij Volwassenen, 2.0, Kooij, & Francken, 2010) in which, following international diagnostic guidelines (Kooij et al., 2010), symptom threshold was set at 4 to reach a diagnosis. Four adults with ADHD experienced between 4 and 6 symptoms, whereas 20 adults experienced 6 or more

symptoms in either or both symptom domains. The ADHD group comprised 9 adults predominantly inattentive type and 15 adults combined type. The Wender Utah Rating Scale (WURS) (Ward, Wender, & Reimherr, 1993), DSM-IV ADHD rating scale (Du Paul, Power, Anastopoulos, & Reid, 1998) and Adult Self Report (ASR, Achenbach & Rescorla, 2003) were administered in both groups to respectively assess presence of childhood ADHD, ADHD manifestation through the lifespan and possible presence of psychiatric disorders. Adults with ADHD using stimulant medication for ADHD symptoms (i.e., 11 adults) were asked to refrain from medication for at least 48 hours before participating in the experiment to control for medication effects.

Exclusion criteria for all participants were history of brain related illness, neurological disorder, suspicion of autism spectrum disorder and estimated full scale IQ below 80, as evaluated by an abbreviated Wechsler Adult Intelligence Scale-III (Wechsler, 1997; Ryan & Ward, 1999). Adults reaching clinical scores on the ASR and scores above cut off for ADHD diagnosis on adult ADHD ratings were excluded from the control group (Table 1).

Table 1. Sample characteristics

	CONTROL (*n* = 20)	ADHD (*n* = 24)
Male/female	11/9	13/11
Age in years	*M* 36.55 (*SD* 11.21)	*M* 34.38 (*SD* 10.21)
Estimated FSIQ	*M* 112.55 (*SD* 11.65)	*M* 108.04 (*SD* 11.30)
Number of EEG segments 2-CRT	*M* 372.20 (*SD* 80.50)	*M* 333.33 (*SD* 89.75)
Number of EEG segments flanker	*M* 520.30 (*SD* 95.77)	*M* 508.71 (*SD* 85.55)
ADHD RS-IV inattention	*M* 4.22 (*SD* 3.35)	*M* 21.22 (*SD* 6.66)
ADHD RS-IV hyperactivity impulsivity	*M* 5.33 (*SD* 2.87)	*M* 19.04 (*SD* 7.34)
ADHD subtype I/C		9/15

Note. *M*: mean, *SD*: standard deviation, FSIQ: Full Scale Intelligence Quotient, ADHD RS-IV: ADHD Rating Scale-IV, I: Inattentive subtype, C: Combined subtype

Procedure

The research protocol was approved by the local ethics committee and written informed consent was obtained from the participants. The protocol involved recordings of resting EEG and execution of a flanker task, a slow paced 2-choice time reaction task, an attention network task and a Simon task, administered in a counterbalanced order. For the purpose of the current study, EEG and performance measures during the 2-CRT and the flanker task were evaluated.

Tasks

2-CRT task. In this task, first a fixation cross was presented with a variable duration (3000 - 4600 ms). Then, the letters X and O were randomly presented for a maximum duration of 1800 ms in the middle of a computer screen, which disappeared from the screen when participants pressed a key. Participants had to press a left key when an X was presented and a right key when an O was displayed. To control for laterality effects, left and right press following X and O were reversed among participants in a counterbalanced order. Finally, a fixation cross was displayed again for 4000 ms. 60 stimuli were presented, half requiring a left and half requiring a right button press.

Flanker task. Executive attention was measured using a modified Eriksen flanker task (Eriksen & Eriksen, 1974; Debener et al., 2005). Participants were asked to evaluate whether a middle arrow of five horizontally presented arrows was directed to the left or right by pressing one of two possible keys in the keyboard. The efficiency of executive attention was measured by evaluating the impact of flankers on reaction time and accuracy. Congruent flankers pointed in the same direction as the target, while incongruent flankers pointed in the opposite direction. At the beginning of each trial, a fixation cross was displayed for 200 ms at the centre of the screen. Subsequently, four flanker arrows were presented for 80 ms, accompanied by the target arrow in the

middle of the flankers 20 ms after the onset of the flankers. This was done to increase the load on interference inhibition. The target arrow was presented for 60 ms, after which a fixation cross was presented with a variable duration (1100 - 1500 ms). The task comprised 480 trials in which half of the trials were congruent, whereas the other half were incongruent trials. Three blocks of 160 trials were administered, in between adults were permitted to take a short break.

EEG recording and processing

During task execution, EEG data were obtained with an electrode cap employing 128 active Ag/AgCl electrodes with average reference, placed according to the 10-5 International System (Oostenveld & Praamstra, 2001). The ground electrode was located in the cap at FPz. Signals were amplified with an open pass-band from DC to 100 Hz with a QuickAmp amplifier (Brain Products, Gilching, Germany) and digitized using Brain Vision Recorder software (version 1.10) with a 500 Hz sampling rate. Analyses of EEG data were performed using Brain Vision Analyzer software (version 2.0.1). EEG data were filtered (band-pass 0.5-50 Hz, notch filter 50 Hz) and segmented (2 s epochs with 1 s overlap). Eye movement correction was conducted according to the Gratton and Coles algorithm (Gratton, Coles, & Donchin, 1983). Segments were rejected from further analyses if absolute difference in amplitudes exceeded 120 μV. The remaining number of segments for analyses did not differ between groups in the 2-CRT task ($F(1, 42) = 2.24$, $p = .14$), nor in the flanker task ($F(1, 42) = 0.18$, $p = .67$) (Table 1). Subsequently, spectral power was calculated using Fast Fourier Transform with a 20% Hanning window and the transformed data were averaged. Absolute power estimates were derived for the theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz) and beta (12.5-25 Hz) band and divided in nine regions: left frontal (AF3, F3, F7), midline frontal (Fz, FCz), right frontal (AF4, F4, F8), left central (T7, C3), midline central (Cz), right central (T8, C4), left posterior (P7, P3, O1), midline posterior (Pz, Oz) and right posterior (P8, P4, O2) (see also Barry et al., 2009). TBR was

calculated by dividing power in the theta band by power in the beta band. A natural logarithmic transform, ln(x), was used to approach normal spreading of the data.

Data analyses

Behavioural performance. For the 2-CRT task, mean reaction time (RT), variability in RT (SD-RT), and percentage errors of commission (%EOC) were compared between groups by separate analyses of variance (ANOVAs) with repeated measures with time-on-task (first, second, third part of testing) as within-subject and group (ADHD, control) as between-subject factor.

For the flanker task, the same analyses were performed for RT and %EOC, with congruency (congruent, incongruent trial) added as an extra within subject factor.

EEG activity. EEG activity in each task was evaluated by separate repeated measures ANOVAs for each frequency band and for TBR with time-on-task (first, second and third part of the respective task), sagittal region (frontal, central, posterior) and lateral region (left, midline, right) as within-subject and group as between-subject factors. When the assumption of sphericity was violated, degrees of freedom were corrected using Greenhouse-Geisser (when $\varepsilon < .75$) or Huynh-Feldt (when $\varepsilon > .75$) estimates of sphericity. Effect sizes were determined by partial eta squared (η^2_p) and interpreted as small (< .06), moderate (.06 - .14), or large (> 0.14) (Cohen, 1988).

Correlation analyses. Pearson correlations were used to evaluate the relationship between EEG parameters and performance measures. In order to reduce the number of tests, only the EEG variables that were found to differ between groups were used in the correlation analyses. According to guidelines, the strength of the correlations was interpreted as small (< .30), moderate (.30 < .50) or large (> .50) (Cohen, 1988). Following van Dongen-Boomsma and colleagues (2010), Bonferroni corrections were not conducted, because the test statistics were assumed to be highly dependent.

RESULTS

Group characteristics

The ADHD-RS IV confirmed that adults with ADHD experienced more problems with inattention ($F(1, 42) = 97.47$, $p < .001$) and hyperactivity/impulsivity ($F(1, 42) = 55.87$, $p < .001$) than typically developing adults. Groups did not significantly differ in terms of estimated full scale IQ ($F(1, 42) = 1.69$, $p = .20$) (Table 1).

Performance data

An overview of the performance data on both tasks is presented in table 2.

2-CRT task. As expected, RT was slower ($F(1, 42) = 6.77$, $p = .01$, $\eta^2_p = .14$) and more variable ($F(1, 42) = 5.70$, $p = .02$, $\eta^2_p = .12$) in adults with ADHD compared to adults without ADHD. Furthermore, the ADHD group tended to commit more EOC than the control group ($F(1, 42) = 3.96$, $p = .05$, $\eta^2_p = .09$). Further, no main time-on-task or group by time-on-task effects were observed.

Flanker task. RT was slower in adults with ADHD than controls ($F(1, 42) = 4.14$, $p < .05$, $\eta^2_p = .09$) and on incongruent than congruent trials ($F(1, 42) = 1197.83$, $p < .001$, $\eta^2_p = .97$). Groups did not significantly differ in terms of %EOC, yet across participants more EOC were made on incongruent than congruent trials ($F(1, 42) = 94.90$, $p < .001$, $\eta^2_p = .69$). The group by congruency effects for RT and %EOC were not significant, respectively ($F(1, 42) = 0.81$, $p = .37$, $\eta^2_p = .02$) and ($F(1, 42) = 0.10$, $p = .75$, $\eta^2_p = .00$), indicating intact interference inhibition in the ADHD group. Across groups, a time-on-task effect emerged for %EOC ($F(2, 82) = 4.72$, $p = .01$, $\eta^2_p = .10$), with more errors made in the second than in the first part of the task ($p = .03$). An interaction between time-on-task and congruency was found as well for %EOC ($F(2, 82) = 3.25$, $p = .04$, $\eta^2_p = .07$). Post hoc analyses revealed a difference in number of errors with time on incongruent trials

($F(2, 84) = 4.16$, $p = .02$, $\eta^2_p = .09$) but not on congruent trials ($F(1.86, 78.04) = 2.34$, $p = .10$, $\eta^2_p = .05$). In specific, more errors were committed on incongruent trials in the second relative to the first part of the testing ($p = .04$), indicating worse interference inhibition with time-on-task. This effect was however the same for both groups, as indicated by the absence of a group x time-on-task x congruency effect ($F(2, 84) = 1.58$, $p = .21$, $\eta^2_p = .04$).

Table 2. Descriptive information on the 2-CRT and flanker task for control adults and adults with ADHD

	Control	ADHD	Group effect	Group x Congruency effect
	M (*SD*)	*M* (*SD*)	*F*(1, 42)	*F*(1, 42)
2-CRT task				
RT	537.47 (113.32)	632.66 (134.73)	6.77*	
SD-RT	109.73 (47.14)	144.33 (63.56)	5.70*	
%EOC	1.58 (2.39)	3.06 (2.49)	3.96+	
Flanker task				
RT			4.14*	0.81
Congruent trials	452.01 (31.34)	476.91 (5.31)		
Incongruent trials	534.47 (32.35)	555.19 (38.54)		
%EOC			0.07	0.10
Congruent trials	0.38 (0.58)	0.39 (0.50)		
Incongruent trials	5.93 (4.14)	5.59 (3.61)		

Note. *M*: mean, *SD*: standard deviation, RT: reaction time, SD-RT: variability in reaction time, %EOC: percentage errors of commission, *$p < .05$, +$p = .05$

EEG

The topographic power distributions for the 2-CRT task and flanker task in each frequency band and TBR are presented in Figure 1.

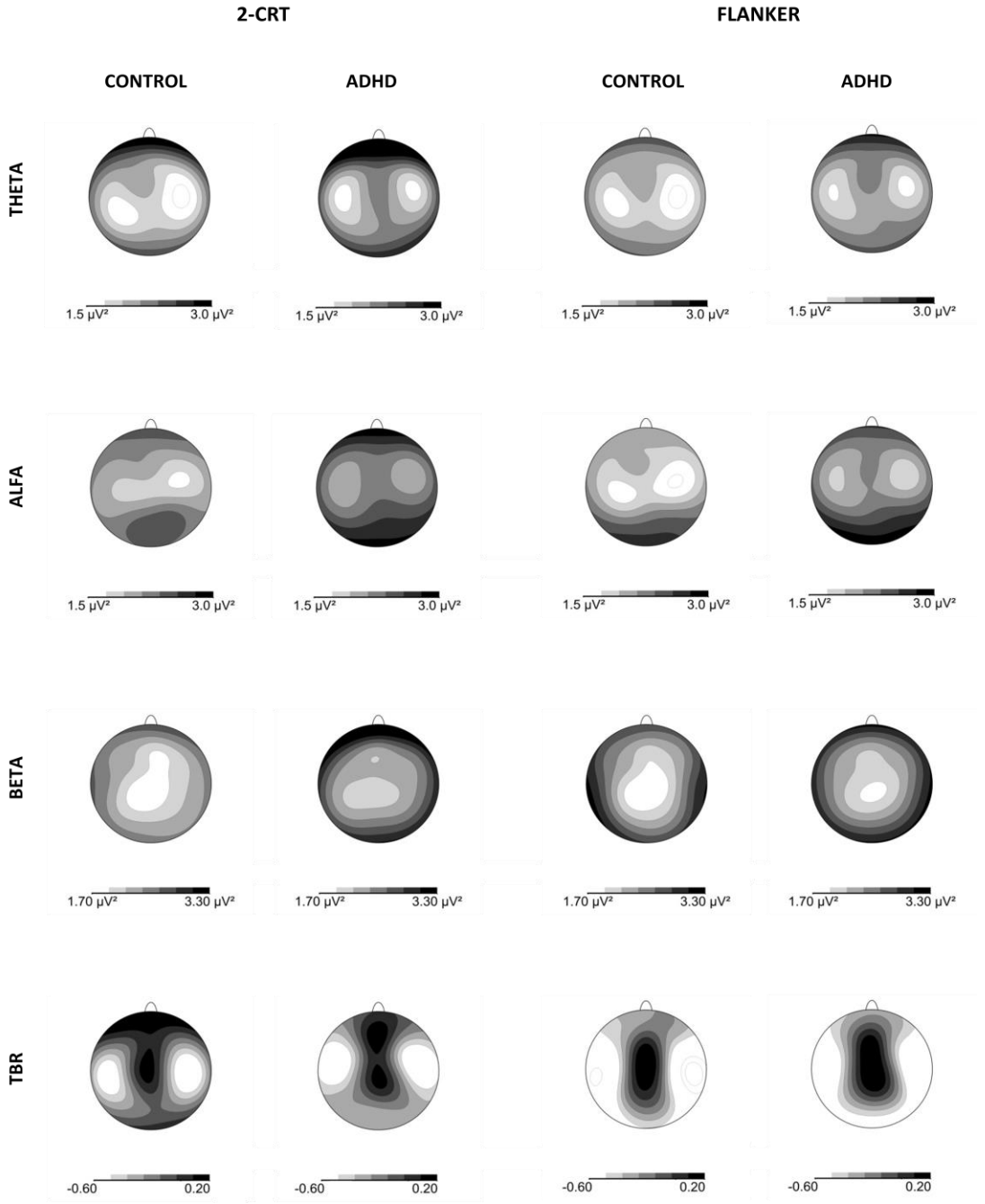

Figure 1. Spectral analysis for 2-CRT and flanker task. Absolute power for theta, alpha and beta frequency bands (lnμV²) and TBR (theta/beta ratio) (ln).

2-CRT task.

Theta power. The main group effect was marginally significant, with higher theta power in the ADHD group ($F(1, 42) = 3.05$, $p = .09$, $\eta^2_p = .07$). A significant group x lateral region effect ($F(1, 42) = 4.12$, $p = .02$, $\eta^2_p = .09$) indicated that theta power at the midline was higher in the ADHD group compared to the control group ($F(1, 42) = 5.96$, $p = .02$, $\eta^2_p = .12$). Time-on-task effects were not detected.

Alpha power. As for alpha power, a trend for an interaction between group and lateral region was found ($F(1, 42) = 2.59$, $p = .08$, $\eta^2_p = .06$). However, post hoc analyses per laterality revealed no significant group effects. Further, a time-on-task effect occurred ($F(1, 42) = 9.03$, $p < .001$, $\eta^2_p = .18$), with an increase in alpha power from the first to the second ($p < .01$) and third ($p < .01$) part of the testing. The time-on-task effect also tended to interact with sagittal region ($F(3.00, 125.95) = 2.15$, $p < .10$, $\eta^2_p = .05$). Follow-up analyses per sagittal region revealed that alpha power increased in each region during testing with the strongest effect at frontal sites.

Beta power. Beta power was higher in the ADHD group than in the control group ($F(1, 42) = 7.57$, $p < .01$, $\eta^2_p = .15$). Time-on-task effects were dependent on sagittal region ($F(3.66, 153.69) = 6.04$, $p < .001$, $\eta^2_p = .13$). Post hoc analyses per sagittal region revealed time effects at frontal derivations ($F(2, 84) = 4.61$, $p = .01$, $\eta^2_p = .10$), indicating higher power at the end compared to the beginning of the task ($p = .03$). Also, a trend for a time-on-task effect appeared at central sites ($F(2, 84) = 2.85$, $p = .06$, $\eta^2_p = .06$). However, follow-up analyses on this effect yielded no further significant results.

TBR. Neither effects involving group were nor a main time-on-task effect was detected for TBR. An interaction was found between time-on-task and sagittal region for TBR ($F(3.46, 145.38) = 2.88$, $p = .03$, $\eta^2_p = .06$). However, time-on-task effects per region did not reach significance.

Flanker task.

Theta power. No effects involving group were detected. Time-on-task effects also did not reach significance for theta power.

Alpha power. Also for alpha power, neither group related effects, nor time-on-task effects were found.

Beta power. As for beta power, an interaction was found between time-on-task and sagittal region ($F(4, 168) = 5.49$, $p < .001$, $\eta^2_p = .12$). Further testing per sagittal area revealed a time-on-task effect at frontal leads ($F(2, 84) = 3.30$, $p = .04$, $\eta^2_p = .07$), indicating a trend for more power at the end compared to the start of the task ($p = .09$). Also, an interaction between time-on-task, sagittal region and lateral region emerged ($F(5.01, 210.50) = 3.74$, $p < .001$, $\eta^2_p = .08$). Follow-up analyses revealed a time-on-task effect at right central region ($F(1.76, 73.79) = 3.95$, $p = .03$, $\eta^2_p = .09$), yet further testing yielded no significant differences between parts of the task.

TBR. A marginally significant interaction between group, sagittal region and lateral region emerged for TBR ($F(4, 168) = 2.36$, $p = .06$, $\eta^2_p = .05$). However, further testing per region revealed no significant group effects. Further, time-on-task effects in TBR differed according to sagittal position ($F(3.34, 140.25) = 3.03$, $p = .03$, $\eta^2_p = .07$). Post hoc analyses did not reveal significant time-on-task effects per region.

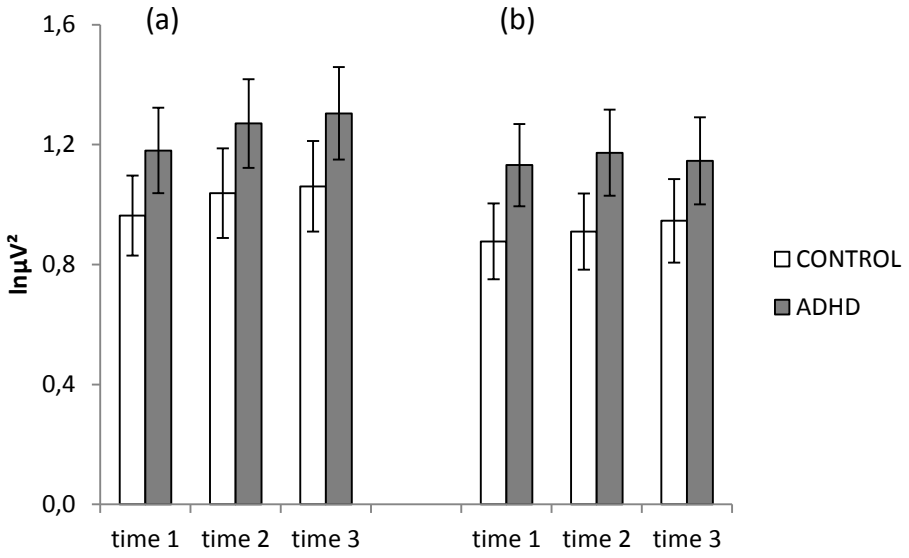

Figure 2. Mean alpha power for all sites with time-on-task for control adults and adults with ADHD for (a) 2-CRT and (b) flanker task. Error bars represent the standard error of the mean.

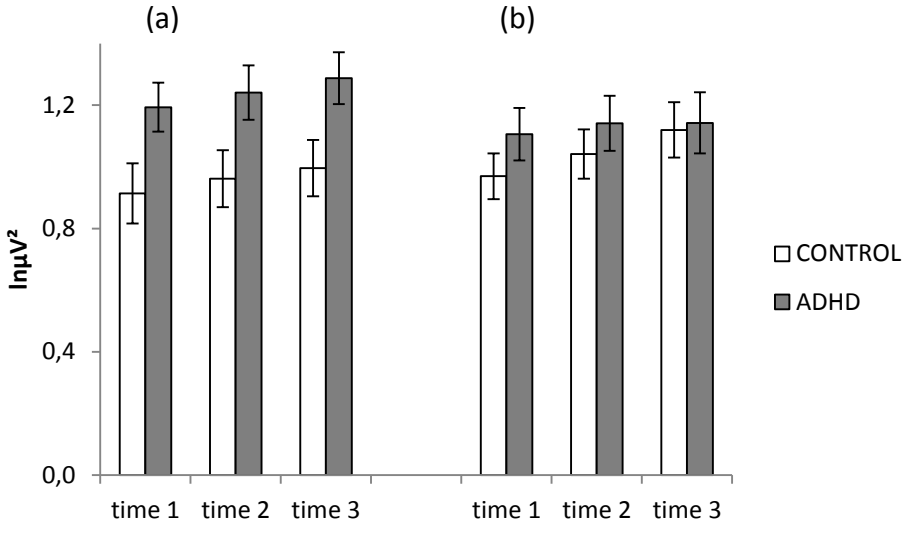

Figure 3. Mean beta power for frontal region with time-on-task for control adults and adults with ADHD for (a) 2-CRT and (b) flanker task. Error bars represent the standard error of the mean.

Additional analyses with sex as a covariate.

Since gender has been documented to affect EEG deviances in ADHD (e.g., Clarke et al., 2003; Dupuy et al., 2013), supplementary analyses were performed with sex as a covariate. Group related findings did not change.

Correlation analyses

Based on the significant interaction effects involving diagnostic status for midline theta and overall beta power in the 2-CRT task, the average power values for respectively midline and all regions were calculated for theta and beta power. Subsequently, those variables were used to correlate with RT, SD-RT and %EOC in the 2-CRT task. In the ADHD group, a significant moderate positive correlation was detected between midline theta power and %EOC (r = .41, p = .04). Although pointing to the same direction, this correlation was not significant and of a small magnitude in the control group (r = .17, p = .47). In addition, all other correlations were small and did not reach statistical significance in either group.

DISCUSSION

The present study examined EEG in adults with ADHD compared to controls during performance of a slow paced 2-CRT task, which required low executive attention and induced a low level of activation, and a moderate paced flanker task, which tapped top-down executive control and induced a moderate activation level. These tasks were chosen to gain more insights into the significance attached to the common observed aberrant theta and TBR in ADHD. One hypothesis is that higher theta or TBR in ADHD is related to impaired activation state in ADHD, as suggested in several publications (e.g., Barry et al., 2009; Clarke et al., 2013) and which would be in accord with the state regulation account of ADHD (Sergeant, 2000; van der Meere, 2005). On the other hand,

high TBR has been proposed to represent impairments in top-down executive control, particularly inhibition (e.g., Schutter et al., 2006; Knyazev, 2007), which parallels the executive dysfunction theory of ADHD (Barkley, 1997).

As for performance measures, with respect to the 2-CRT task, adults with ADHD were found to be slower and more variable in their responding and tended to make more errors than control participants. This is in line with a large number of studies using a variety of tasks, showing worse performance in ADHD when stimuli were presented at a slow rate (e.g., Brown & Vickers, 2004; Leung et al., 2000; Metin et al., 2012, for a meta-analysis; Rubia et al., 1999; Scheres et al., 2001; Wiersema et al., 2006a,b). The finding that performance in ADHD is highly sensitive to presentation rate of stimuli has been explained in terms of state regulation difficulties (van der Meere, 2005). In specific, as slow event rates induce a state of underactivation (Sanders, 1983), it has been suggested that individuals with ADHD are easily under-activated and have difficulty in adjusting their under-activated state because of insufficient effort allocation (Johnson, Wiersema, & Kuntsi, 2010; Wiersema et al., 2006a,b).

Regarding the flanker task, in accord with existing research (for a review, see Mullane, Corkum, Klein, & McLaughlin, 2009; Chang, Davies, & Gavin, 2009; McLoughlin et al., 2009), slower responding and decreased accuracy were found in this task when targets were surrounded by conflicting flankers, which indicates that additional attentional processing was required to filter out interfering information (Mullane et al., 2009), and hence that the task efficiently tapped executive control. Yet, importantly, groups did not differ in congruency effects, which corresponds with literature in adults with ADHD (Chang et al., 2009; McLoughlin et al., 2009) and suggests intact interference inhibition in the ADHD group (Johnstone & Galetta, 2013). Instead adults with ADHD were found to be slower, independent of congruency condition, as found before (Chang et al., 2009; McLoughlin et al., 2009). Performance deteriorated during task execution, especially on incongruent trials, indicating worsening of interference inhibition with task

duration. However importantly, groups did not differ in this respect, suggesting no sustained attention deficit in our sample of adults with ADHD, which is in line with other research (Schachar, Logan, Wachsmuth, & Chajczyk, 1988; Stins et al., 2005; Tucha et al., 2010).

Broadly in accord with the findings on the behavioural level, EEG deviances in ADHD were found during performance on the slow paced 2-CRT task, but not the flanker task. More specific, adults with ADHD showed increased theta and beta power when performing the task that induced a low activation level and required minimal executive functioning (i.e., 2-CRT), whereas no deviances were observed in the task with a high load on executive control and a regular activation level (i.e., the flanker task). This indicates that EEG deviances in ADHD may be task-dependent and reflect impairment in activation state rather than executive control. This appears to be confirmed by the finding of a moderate positive correlation between theta power and errors of commission in the 2-CRT task in adults with ADHD. Yet, this association was small in the control group, suggesting a possible difference in neural organization in adults with ADHD relative to controls (Loo et al., 2009).

Elevated theta during task performance in ADHD has been reported before (El-Sayed et al., 2002; Janzen et al., 1995; Mann et al., 1992; Rasey et al., 1999). As theta power has repeatedly been found to increase during tasks with a higher cognitive load, enhanced theta power during task execution has often been explained in terms of an increase in mental activity to perform a difficult task (e.g., Gevins, Smith, McEvoy, & Yu, 1997; Onton, Delorme, & Makeig, 2005; Sammer et al., 2007; Sauseng, Hoppe, Klimesch, Gerloff, & Hummel, 2007). This modulation of theta has been noticed to appear at the frontal midline region of the scalp and has been associated with activity in the anterior cingulate cortex (Peterson & Posner, 2012). In light of the present data, it seems however unlikely that the elevated theta power in ADHD in the 2-CRT task reflects increased mental activity related to task difficulty, as actually the cognitive load in the 2-

CRT task was rather low, especially when compared with the flanker task. Moreover, the increased theta power in our ADHD group was not limited to frontal midline theta power. With regard to this topographical factor, a more generalized increase in theta activity is known to be a marker of drowsiness (e.g., Barwick, Arnett, & Slobounov, 2012; Jödicke et al., 2013; Lal & Craig, 2001; Oken, Salinsky, & Elsas, 2006). Hence, the higher theta in adults with ADHD during performance on the slow 2-CRT task may rather reflect an under-activated state (decreased readiness to respond), which may have resulted in inadequate processing of the stimuli, consequently leading to a higher rate of commission errors.

In addition to elevated theta power, enhanced beta power was found in the ADHD group during 2-CRT task performance. Up to date, the functional significance of power in the beta frequency range seems to be the least well understood (Engel & Fries, 2010). Nevertheless, beta power has frequently been reported to reflect cortical activity related to higher order processing (Barry, Clarke, Johnstone, Magee, & Rushby, 2007; Kropotov, 2009; Loo et al., 2009). Furthermore, elevated power in the beta band has been interpreted as representing compensatory effort to counteract a low vigilance level (Corsi-Cabrera, Sánchez, del-Río-Portilla, Villanueva, & Pérez-Garci, 2003; Fischer, Langner, Birbaumer, & Brocke, 2008; Kiroy, Warasawskaya, & Volyov, 1996; Smit, Eling, Droogleever Fortuyn, & Coenen, 2005). From that, the finding of increased beta power may reflect increased effort allocation in adults with ADHD in order to counteract their under-activated state (Hockey, 1997; Mulder, 1986; Sanders, 1983, 1998). Other studies also indicated difficulty with effort allocation in ADHD during slow presentation rates, however there less effort allocation in ADHD was noticed (Börger & van der Meere, 2000; Wiersema et al., 2006a,b). Yet, it should be noted that in those studies time-on-task effects were not investigated. Hence, it may be possible that failed attempts to upregulate activation level led participants with ADHD to discontinue investing extra effort, while in the current study, adults with ADHD kept allocating additional

compensatory effort. Also, a direct comparison between studies is hampered by the use of different measures (i.e., beta, heart rate variability, P3 event related potential component) to evaluate effort allocation.

While in some studies different time-on-task effects on EEG activity have been reported in ADHD compared to control adults (Loo et al., 2009; Rasey et al., 1999), this was not the case in the present study, which is in line with our findings on the performance level. Alpha power increased during the course of the 2-CRT task in both groups, which is in accord with existing literature (Barwick et al., 2012; Gevins et al., 1997; Loo et al., 2009; Smith, McEvoy, & Gevins, 1999), and may indicate a decrease in alertness (e.g., Barwick et al., 2012; Oken, Salinsky, & Elsas, 2006) or attentional processing (e.g., Laufs et al., 2003; Willeford, Ciuffreda, Yadav, Ludlam, 2013) with time. As vigilance or attention levels may drop earlier in boring tasks with long inter stimulus intervals, this may explain why an alpha increase with time was only observed in the 2-CRT task. Alternatively, the inclusion of breaks in the flanker task may have contributed to this. In both tasks and in both groups, an increase of frontal beta with task duration was noticed, which might reflect increased effort allocation to maintain meeting task demands. Crucially and most important however, is the fact that time-on-task effects could not differentiate adults with ADHD from controls.

Some considerations have to be made with respect to the interpretation of the results. First, assigning specific functional roles to different frequency bands remains difficult because throughout literature, they have been associated with a variety of states and cognitive phenomena (Loo & Makeig, 2012). Including additional measures such as subjective ratings of alertness or task-related effort as well as other physiological measures (i.e., skin conductance level to capture autonomic arousal, heart rate variability) in future studies, may help clarifying the functional significance of EEG deviances in ADHD. Next, although a head to head comparison was made between two possible hypotheses regarding deviant EEG, especially theta and TBR, in ADHD, the use

of an orthogonal research design would have been more appropriate to formulate firm conclusions. Finally, in the literature the concepts of arousal and activation have been defined and interpreted in different ways, which may hamper interpreting results. 'Activation' as used by Barry and colleagues (2009) and as formulated in the state regulation account may not fully overlap and future studies are warranted to investigate this issue. However, a common factor in each conceptualization of 'activation' is the reference that is made to an energetic state. Therefore, we argue that it is safe to say that the EEG deviances in adults with ADHD in the current study were related to energetic state factors.

Despite these limitations, the current findings indicate that EEG deviances in ADHD are task-dependent, since aberrant EEG activity was not consistently found across both tasks. This may indicate that EEG deviances in ADHD are not to be seen as a fixed hallmark but rather as a dynamic characteristic that fluctuates across states and in response to environmental contexts. This corresponds with models that emphasize the dynamic, rather than the fixed nature of ADHD and especially the role of contextual and state factors in determining deficits (Sonuga-Barke et al., 2010). Future studies are needed to confirm the findings of the present study and to shed more light on the dynamic nature and significance of EEG deviances in ADHD.

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CHAPTER 7

GENERAL DISCUSSION

The aim of the present dissertation was to gain more insights into the nature and functional significance of quantitative electroencephalographic (EEG) deviances in attention-deficit/hyperactivity disorder (ADHD). To this end, several empirical studies were conducted, in which EEG activity was compared between individuals with ADHD and typically developing individuals. In this final chapter, the goals of the dissertation will be briefly recapitulated and the most important findings will be summarized and discussed. In addition, scientific and clinical implications of the findings will be outlined. Finally, some limitations of the conducted studies and suggestions for future research will be formulated.

RECAPITULATION OF THE RESEARCH GOALS

In recent years, there has been an increasing interest in the use of quantitative EEG for clinical purposes in ADHD, particularly with respect to the diagnosis and treatment of the disorder. From a translational perspective, it is imperative that clinical practice is grounded in and informed by knowledge on the psychopathophysiology of the disorder (Sonuga-Barke & Halperin, 2010). This emphasizes the importance of gaining more insights into the nature, stability and significance of quantitative EEG deviances in ADHD, which was aimed for in the current dissertation. As the behavioural and cognitive problems that are associated with ADHD are well-known to fluctuate across states and settings (Sonuga-Barke, Wiersema, van der Meere, & Roeyers, 2010), a special focus of this dissertation was to investigate whether this state and context dependent nature of the disorder would also be mirrored in EEG activity. Therefore, EEG in children as well as adults was recorded in a variety of conditions, which differed in state and context-related features. This leads to the second goal of this dissertation, which was to increase knowledge on the significance that is attached to the possible EEG deviances in ADHD. Several EEG-based models have been developed to explain those deviances, in which the typical expressed EEG abnormalities in ADHD (i.e., increased theta and elevated theta to beta ratio (TBR) (for a review, see Barry & Clarke, 2009)) are related to either maturational delay (e.g., Satterfield, Schell, Backs, & Hidaka, 1984), underarousal (e.g., Lubar, 1991), impaired activation (e.g., Barry, Clarke, Johnstone, McCarthy, & Selikowitz, 2009), or reduced cortical control over subcortical substructures (e.g., Schutter, Leitner, Kenemans, & van Honk, 2006). These theories have been examined across the studies presented in this dissertation. Moreover, an attempt was made to integrate insights from the EEG-based models with knowledge from several well-investigated neuropsychological models of ADHD, as they appear to overlap at some points.

INTEGRATION OF THE MAIN FINDINGS

Stability of EEG deviances in ADHD

Theta power and theta to beta ratio as trait-like markers for ADHD? The most common findings in EEG studies among children, adolescents and adults are elevated theta power and an increased TBR in ADHD (see Barry & Clarke, 2009; Barry, Clarke, & Johnstone, 2003; Dupuy, Barry, Clarke, McCarthy, & Selikowitz, 2013 for reviews). The robustness of these findings, however, has to be questioned since several studies could not detect significant abnormalities in theta and/or TBR in ADHD, neither in resting conditions (Coolidge, Starkey, & Cahill, 2007; Liechti et al., 2013; Loo et al., 2013; Nazari, Wallois, Aarabi, & Berquin, 2011; Ogrim, Kropotov, & Hestad, 2012; Poil et al., 2014; Swartwood, Swartwood, Lubar, & Timmermann, 2003; van Dongen-Boomsma et al., 2010) nor during task performance (Loo et al., 2009; Nazari et al., 2011; Swartwood et al., 2003; White, Hutchens, & Lubar, 2005). This inconsistency is confirmed by the findings in the present dissertation. While elevated theta power was apparent in certain contexts, it is not to be regarded as a robust characteristic of individuals with ADHD. As for TBR, in general no deviances were detected in the whole ADHD group, though in one study elevated TBR was found in the ADHD inattentive subtype.

Deviances in alpha and beta power. Regarding deviances in the alpha and beta frequency bands, so far mixed results have been published.

As for alpha power, most resting EEG studies refer to decreased alpha (Barry et al., 2009; Clarke, Barry, McCarthy, & Selikowitz, 1998; Clarke, Barry, McCarthy, & Selikowitz, 2002a; Clarke et al., 2003a; Dupuy, Clarke, McCarthy, & Selikowitz, 2011) but increased alpha (Chabot & Serfontein, 1996; Clarke et al., 2011b; Poil et al., 2014) and equivalent alpha power to control groups (Loo et al., 2010; Shi et al., 2012) have also been observed. Likewise, alpha was found to be reduced (Loo et al., 2009), enhanced (White et al., 2005) or normal (Nazari et al., 2011; White et al., 2005) in ADHD during

task execution. Accordingly, the present findings do not indicate that individuals with ADHD are characterised by stable deviances in alpha power. Deviation in this frequency band was only found in terms of less alpha suppression to eye opening in children with ADHD without comorbid oppositional defiant disorder (ODD) or conduct disorder (CD).

Likewise, beta power was often found to be reduced in ADHD in resting conditions (Clarke et al., 1998, 2002a, 2003a; Dupuy et al., 2011; Shi et al., 2012), although several studies failed to find group differences (Liechti et al., 2013; Loo et al., 2010) or even detected higher beta power in (a subgroup of) ADHD (Chabot & Serfontein, 1996; Clarke et al., 1998; Clarke, Barry, McCarthy, & Selikowitz, 2001a; Clarke et al., 2013; Poil et al., 2014). One study reported reduced beta power (Rasey, Craig, & Lubar, 1999), whereas others did not demonstrate deviances in ADHD during task execution (Loo et al., 2009; Nazari et al., 2011). These inconsistencies were also reflected in our findings. Depending on the condition, reduced, normal as well as enhanced beta power was found in ADHD(-inattentive subtype).

Conclusion regarding the stability of EEG deviances in ADHD. In all, the findings suggest that EEG deviances in ADHD are not to be regarded as fixed, stable characteristics, rather are to be interpreted in a dynamic, state- and context-related framework. Moreover, the heterogeneity in ADHD, as reflected in the clinical presentation of symptomatology (i.e., ADHD subtypes) and the presence of comorbid ODD/CD, appears to contribute to the manifestation of EEG deviances in ADHD. This will be further discussed in the following sections.

Interpretations of the (disparity in) EEG deviances in ADHD

Maturational factors affecting EEG deviances in ADHD. In chapter 2, it was investigated whether a delay in EEG maturation, which is considered to be a dynamic factor related to development, may account for EEG deviances in ADHD. In one of the earliest accounts of EEG deficits in ADHD, the commonly elevated theta and TBR and

reduced beta power in ADHD are interpreted as reflecting a lag or delay in cortical development (Clarke et al., 1998; Lazzaro et al., 1998; Satterfield et al., 1984). An inherent implication of the maturational lag model is that EEG abnormalities in ADHD are expected to taper off with age (Barry & Clarke, 2009). It should be noted that this account was basically developed to explain EEG deviances in children with ADHD and that it originated when little information was available on EEG activity in adult ADHD. With the increment of EEG studies in adults with ADHD in the last decade, the maturational delay hypothesis has become less influential in the literature, as several studies established EEG abnormalities in adults similar to those in children, which argues against the model.

In the present dissertation, elevated TBR and reduced relative beta power were observed in ADHD across the lifespan, without an interaction between age and diagnostic status. Yet, those deviances were only detected in individuals with the inattentive subtype of ADHD. These findings are in line with another study, also failing to detect age-dependent EEG abnormalities in ADHD (Liechti et al., 2013), although it should be mentioned that in that study, no EEG divergence was found at all in ADHD. In contrast, an earlier study found theta power to be elevated across age groups, while the difference in beta power in ADHD compared to controls decreased with increasing age (Bresnahan, Anderson, & Barry, 1999).

Our findings do not support the hypothesis of a maturational lag that is caught up in adulthood to explain EEG deviances in individuals with ADHD, as a persistent aberrant EEG picture was found across the entire lifespan. Further, our results seem to confirm the notion of a stable pattern of EEG deviances across the lifespan, as the same spectral measures were found to be aberrant in ADHD across age groups. However, this is not in line with a recent study, in which activity in different frequency bands was found to be distorted in children compared to adults with ADHD (Poil et al., 2014). More

research is needed to clarify this, as a comparison between studies is being hampered because of differences in the methodologies that are used to evaluate EEG activity.

The cross-sectional design of the study warrants cautiousness in interpretations, as it does not allow to directly evaluate developmental changes of individuals. In this respect, a possible confounding factor may be that the EEG profile of children with persistent ADHD differs from that of children who remit in adulthood (Clarke et al., 2011b). Ideally, longitudinal studies should be conducted, as these are more feasible to delineate the developmental course of EEG deviances in ADHD. While no clear evidence could be found for a transient maturational lag underlying EEG deviances in ADHD, it is still possible that EEG activity in ADHD is characterised by an atypical developmental pattern (Poil et al., 2014), which could be addressed by evaluating EEG activity at more than two time points that are more closely spaced (Doehnert, Brandeis, Imhof, Drechsler, & Steinhausen, 2010).

Contextual and state factors affecting EEG deviances in ADHD.

The influence of intervening cognitive effort on resting EEG. Several studies in typically developing adults have demonstrated that resting EEG patterns change after task execution, indicating that intervening cognitive effort may provoke state changes (Smit, Eling, & Coenen, 2004; Smit, Eling, Hopman, & Coenen, 2005; Tanaka et al., 2012). In light of the dynamic contextual nature of deficits in ADHD, this raised the question whether possible EEG deviances in ADHD would be stable across conditions before and after cognitive effort and to what extent altered state-related changes in EEG activity would be detected in ADHD after task execution. So far, to our knowledge, only one study addressed this, be it in an adult sample, and found increased beta power in controls but not in individuals with ADHD after cognitive effort (Koehler et al., 2009). In chapter 3, we evaluated EEG activity in children with and without ADHD before and after execution of three n-back tasks, which were presented in a counterbalanced order. No evidence was found for abnormal EEG activity in ADHD across conditions. After

cognitive effort, EEG changes were observed in both groups, providing evidence for state-related changes after task execution. However, children with ADHD did not differ from typically developing children in this respect.

The influence of arousal. One of the most prominent accounts of elevated theta and TBR claims that these abnormalities represent a state of underarousal (e.g., Lubar, 1991; Mann, Lubar, Zimmerman, Miller, & Muenchen, 1992), although this has recently been debated because those parameters were not found to correlate with a well-known measure of autonomic arousal (i.e., skin conductance level). Instead, alpha power was established to be a good indicator of arousal (Dupuy, Clarke, Barry, Selikowitz, & McCarthy, 2014). As several broad theoretical constructs of ADHD emphasize arousal problems to be a basic mechanism in ADHD (i.e., optimal stimulation theory (Zentall & Zentall, 1983), state regulation theory (Sergeant, 2005; van der Meere, 2005), moderate brain arousal model (Sikström & Söderlund, 2007)), a few studies in this dissertation focussed on arousal states in ADHD.

In chapter 4, EEG activity in children with and without ADHD was compared between an eyes closed and an eyes open condition, which represent two different states of arousal. Opening of the eyes is namely a procedure that is known to result in an arousal increment (Barry, Clarke, Johnstone, Magee, & Rushby, 2007; Hüfner et al., 2009). Some recent studies investigating both eyes closed and eyes open resting EEG in children as well as adults indicated that deviances in ADHD are more pronounced in the eyes closed condition (Lansbergen, Arns, van Dongen-Boomsma, Spronk, & Buitelaar, 2011; Loo et al., 2013; Woltering, Jung, Liu, & Tannock, 2012) and that EEG modulation, especially alpha attenuation, between the conditions is disturbed in ADHD (Fonseca, Tedrus, Bianchini, & Silva, 2013; Loo et al., 2010; van Dongen-Boomsma et al., 2010; Woltering et al., 2012). The latter was confirmed in our study, denoting not only a smaller alpha but also a slighter theta attenuation from eyes closed to eyes open condition in children with ADHD without comorbid ODD/CD. It should be noted that the

effects were not accounted for by a group divergence in EEG activity in either the eyes closed or eyes open condition, but resulted from an impaired transition between the conditions.

In chapter 5, resting EEG without and with exposure to pink noise were compared between adults with ADHD and controls, hereby elaborating on the notion of possible arousal dysfunction in ADHD. That is, according to the moderate brain arousal model, individuals with ADHD are characterised by a state of underarousal, which may possibly be restored by presenting external environmental noise (Söderlund, Sikström, & Smart, 2007). No EEG differences were detected between groups at baseline condition, yet less theta suppression with noise exposure was observed in adults with ADHD, resulting in an elevated midline theta power in ADHD in the noise condition. Both groups showed a decrease in alpha power with noise. Remarkably, no EEG changes between conditions were detected when the noise condition preceded the condition without noise, which was speculated to be caused by an after effect of the noise on subsequent resting EEG.

The influence of activation. More recently, elevated TBR in ADHD has been reconceptualized in terms of impaired functionality of cortical activation (Barry et al., 2009). Compatible with the state regulation account of ADHD, which postulates that individuals with ADHD have difficulties in regulating their activation state in suboptimal conditions (Sonuga-Barke et al., 2010), we addressed this hypothesis by evaluating on-task EEG activity in adults with and without ADHD during a cognitive low demanding 2-choice reaction time task with a slow event rate, inducing a low activation level in the participants. On a behavioural level, adults with ADHD responded slower and more variable than controls and tended to commit more errors, which is in accord with literature showing worse performance during conditions with slow event rates in ADHD (e.g., Brown & Vickers, 2004; Leung, Leung, & Tang, 2000; Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012, for a meta-analysis; Rubia, Taylor, Taylor., &

Sergeant, 1999; Scheres, Oosterlaan, & Sergeant, 2001; Wiersema, van der Meere, Antrop, & Roeyers, 2006a; Wiersema, van der Meere, Roeyers, Van Coster, & Baeyens, 2006b). On an EEG level, adults with ADHD expressed elevated theta power, especially at midline derivations, which was found to correlate positively with commission errors. In addition, enhanced beta power was detected in the ADHD group.

Reduced top-down control. Another theoretical approach explains increased TBR as reflecting reduced cortical control over subcortical structures (Schutter et al., 2006; Knyazev, 2007), hence suggesting higher TBR in ADHD to reflect a tendency to prefer activation over inhibition. This explanation parallels the executive dysfunction theory of ADHD, which relates the core problem of ADHD to impairments in executive functioning (i.e., top down executive control), especially in response inhibition (Barkley, 1997). To investigate this account, EEG was recorded in adults with and without ADHD during performance of a flanker task, which required attentional top-down control. Although adults with ADHD had slower reaction times than typically developing adults, they did not deviate from controls in terms of congruency effects. In fact, in both groups strong congruency effects were detected, suggesting that additional attention was required to deal with conflicting information during task performance, as hypothesized (Mullane, Corkum, Klein, & McLaughlin, 2009). The absence of finding group differences for the conflict-effect is in agreement with literature in adults with ADHD (Chang, Davies, & Gavin, 2009; McLoughlin et al., 2009) and is not particularly surprising. Research has shown that performance on executive tasks in ADHD may vary depending on several factors, such as task characteristics (i.e., event rate rate of the stimuli (Wiersema et al., 2006a,b)) and contextual factors (e.g., Sonuga-Barke et al., 2010). Regarding on-task EEG activity, also no group differences were detected. Noteworthy, in the same sample of adults, adults with ADHD expressed a differential EEG pattern in a task inducing low activation, as mentioned before.

Conclusions regarding the contextual and state factors affecting EEG deviances in ADHD. Altogether, the findings support the notion that the expression of EEG deviances in ADHD is related to state and contextual factors. In broad outline, individuals with ADHD could be best distinguished from typically developing individuals in situations in which arousal and activation states were manipulated.

Theta power. Throughout the studies that addressed modulations in energetic state, mainly the activity in the theta band was found to be distorted. In specific, we observed elevated theta power in a low activation condition (i.e., slow paced 2-choice reaction time task) and reduced theta reactivity to arousal enhancing procedures (i.e., eye opening and noise exposure). The association between distorted theta power during a state of low activation appears to fit with the EEG-based model postulating impaired activation to be associated with this deviance (Barry et al., 2009). The model is however extended with the notion of an anomalous activation *mechanism* in ADHD. This is highly compatible with the state regulation account of ADHD (Sergeant, 2005; van der Meere, 2005), which is grounded in the cognitive-energetic model of Sanders (1983) and proposes that difficulties in ADHD are context dependent and arise in situations that induce suboptimal states. In this respect, it is possible that the moderate event rate in the flanker task did not produce a suboptimal activation state in adults with ADHD, leading to the lack of finding EEG group differences in that condition. In addition, regarding the absence of finding altered EEG changes in ADHD after cognitive effort, the question is raised whether different intervening tasks, for instance tasks that evoke low activation levels, may provoke abnormal EEG modifications in ADHD.

As for the reduced theta modulation in arousal enhancing conditions, some studies recommend cautiousness in interpreting theta power as an index of arousal, given its inconsistent association with skin conductance level (Dupuy et al., 2014; Lim et al., 1996), which is considered to be a reliable indicator of autonomic arousal (Critchley, 2002). However, recently, the validation of electrodermal activity to be the most

reliable indicator of arousal has been discussed, as it only mirrors parasympathic activity, and ideally both parasympathic and sympathic activity should be mapped to get a complete picture of autonomic arousal (Olbrich et al., 2011). Even so, an alternative explanation for the reduced attenuation of theta power in the arousal enhancing conditions may be that this effect reflects altered processing of the respectively visual and auditory stimulation with eye opening and noise exposure. With respect to the latter, maybe individuals with ADHD require more stimulation to modulate EEG activity than was offered. However, the same level of noise was used as in experiments establishing beneficial effects of noise on task performance in ADHD. Regarding this, it might be possible that task characteristics interfere with the level of noise required to modulate EEG activity in ADHD. This should be explored in further work.

Anyhow, from a more broad perspective, throughout the literature, enhanced activity in the theta band has traditionally been associated with a state of reduced alertness (e.g., Barwick, Arnett, & Slobounov, 2012; Jödicke et al., 2013; Lal & Craig, 2001; Oken, Salinsky, & Elsas, 2006). Considering this, the present findings may generally indicate that individuals with ADHD have more difficulties in changing from a less alert to a more alert state (chapter 4 and chapter 5), and are more easily brought into a state of drowsiness (chapter 6) when not enough activation is present. In all, the findings appear to suggest less adaptation or regulation in the theta frequency band in ADHD.

Alpha power. The notion of an altered state modulation in ADHD was also reflected in the alpha frequency band. The suppressed alpha attenuation with eye opening may possibly be interpreted as reflecting a deficiency in arousal modulation in ADHD as alpha power has been suggested to be an indicator of arousal (e.g., Dupuy et al., 2014).

Beta power. In the low activation condition, besides elevated theta power, also enhanced beta power was detected in ADHD. Several studies have associated beta

power with compensatory effort to counteract a low vigilance level (Corsi-Cabrera, Sánchez, del-Río-Portilla, Villanueva, & Pérez-Garci, 2003; Fischer, Langner, Birbaumer, & Brocke, 2008; Kiroy, Warasawskaya, & Volyov, 1996; Smit, Droogleever Fortuyn, Eling, & Coenen, 2005). This leads to the suggestion that adults with ADHD tried to compensate for a state of underactivation by producing more global beta activity, although this approach appeared not to be successful. Altered effort allocation in ADHD during tasks with slow event rates has been described before, yet in terms of reduced investment of effort (Börger & van der Meere, 2000; Wiersema et al., 2006a,b). However, a direct comparison with other studies is being hampered because different physiological measures were used to evaluate effort (i.e., beta, heart rate variability, P3 event related potential component). That is, while beta power is a tonic measure, P3 and heart rate variability are both phasic indicators of effort. In this respect, it might still be possible that, although adults with ADHD on the whole invested more effort in the slow paced task than control adults, the specific event-related allocation of extra effort was impaired in our ADHD group.

Underarousal as a core characteristic of ADHD? Our findings indicate that individuals with ADHD are not characterised by a baseline state of underarousal because in neither "low arousal" baseline resting condition of the experiments, aberrant EEG activity was found in ADHD. EEG abnormalities were only found when an increase in arousal level was induced, showing less EEG responsivity to the arousal enhancing procedure in ADHD. This appears to run counter the optimal stimulation theory (Zentall & Zentall, 1983) and the moderate brain arousal model (Sikström & Söderlund, 2007), which would predict deviation in the condition with the lowest level of arousal, being corrected in the arousal enhancing condition. In this respect, it may be suggested that the duration of the EEG recordings (i.e., 3 minutes) was not sufficient to elicit a state of underarousal in individuals with ADHD. In some other studies that do find EEG abnormalities during baseline resting conditions, traditionally a comparable number of

segments was used to analyze EEG activity, however, the epochs were selected out of up to 20 minutes of recording (Clarke et al., 2002a), which might be more provocative for suboptimal energetic states. This may partly explain some inconsistent findings between studies.

Potential sources of EEG heterogeneity in ADHD.

The findings of the present dissertation indicate that not only state and contextual factors affect EEG deviances, but also that hetereogeneity in ADHD may have mediating effects on the expression of aberrant EEG activity in ADHD.

Subtypes. So far, disparate findings have been reported regarding the differentiation of EEG profiles between ADHD subtypes. Moreover, research that focusses on subtypes has been limited to a comparison between ADHD-inattentive subtype (ADHD-I) and ADHD-combined subtype (ADHD-C). While most studies have documented EEG deviances in both subtypes compared to control groups, inconsistent findings have been reported on EEG divergence between the subtypes. In specific, whereas some studies have documented that EEG profiles are equivalent in ADHD-I and ADHD-C (Hermens et al., 2004; Loo et al., 2010; Monastra, Lubar, & Linden, 2001), others reported that individuals with ADHD-I express a pattern of abnormalities between ADHD-C and control subjects (Clarke et al., 1998; Dupuy et al., 2011). Once, the ADHD-I group has been established to deviate more from a control group compared to the ADHD-C group (Loo et al., 2010), which is in line with the findings of this dissertation. Unfortunately, the divergence between ADHD subtypes was only examined in the study with the combined child and adult group, in which only an eyes closed condition was compared between ADHD and non-ADHD groups, as the sample sizes were insufficient to perform these analyses in the studies in the separate age groups. EEG divergence in our study could not be explained by variations in symptom severity of attention problems between the subtypes (Diamond, 2005; Milich, Balentine, & Lynam, 2001), which led to the suggestion that different neural circuits underlie problems in

ADHD-C and ADHD-I. However, besides the fact that our data could not unequivocally support this, a recent meta-analysis found minimal support for classifying ADHD-I and ADHD-C as distinct pathologic entities (Willcutt et al., 2012). A possible confounder in investigating ADHD subtypes is the fact that the classification of subtypes is based on a categorical decision, using the number of symptoms in the separate symptom dimensions to assign subtypes. This means that, especially in the group of participants with ADHD-I, there is a possible large inter-individual variability with some individuals with ADHD-I showing very few symptoms of hyperactivity/impulsivity, while others expressing a subclinical picture of ADHD-C. Hence, the make-up of the sample of individuals with ADHD may highly differ between studies, which impedes a proper comparison between datasets.

Comorbid ODD/CD. As for possible mediating effects of comorbid oppositional defiant disorder (ODD) and conduct disorder (CD) on EEG deviances in ADHD, it has to be noted that among the few studies that investigated this, only one study has documented on a broad range of EEG parameters (i.e., Clarke et al., 2002a). While one study established that comorbidity with ODD/CD has an enlarging effect on TBR deviance in children with ADHD (Loo et al., 2013), another study did not detect this effect and instead reported that focal theta abnormalities were more pronounced in an ADHD only group than in an ADHD group with ODD/CD comorbidity (Clarke et al., 2002a). Yet another study suggested no impact of comorbid ODD/CD on EEG deviances in ADHD (Liechti et al., 2013).

The inconsistent results among studies is also represented in the current dissertation, in which mixed findings on this topic emerged. In chapter 4, a divergent alpha and theta response to eye opening was only detected in a group of children with ADHD without comorbid ODD/CD. Although not reported in chapter 3, the influence of comorbid ODD/CD on EEG changes after cognitive effort was also explored. Yet, there, comorbid disorder did not appear to have a significant impact on the results, as all the

effect sizes remained in the same range when analysing the data with exclusion of the children with comorbid ODD/CD. This raises the question whether the influence of comorbidity on the detection of EEG differences in ADHD depends on state-related factors. In specific, whereas opening of the eyes is associated with a modulation of arousal, a change in arousal state might not have been elicited by the execution of tasks. As for arousal differences between children with ADHD only and children with comorbid ODD, some studies have addressed differences in skin conductance level between those groups. Lower skin conductance has been demonstrated in both groups compared to a control group, implying arousal deficiencies in ADHD. Yet, differences in electrodermal activity between the ADHD groups with and without comorbidity with ODD have not been validated, suggesting comparable arousal deficiencies in ADHD only and ADHD with comorbid ODD (Snoek, Van Goozen, Matthys, Buitelaar, & Van Engeland, 2004; van Lang et al., 2007). Currently, there is still disagreement about whether comorbid oppositional symptoms in ADHD should be considered as a component of ADHD or whether ADHD+ODD/CD represents a distinct disorder (Connor, Steeber, & McBurnett, 2010), as also defined in the International Classification of Diseases and Related Health Problems classification system (ICD-10, World Health Organisation, 2008). However, a direct comparison of the ADHD only and the comorbid group was hampered by the small number of children showing comorbid ODD/CD, which makes it difficult to draw reliable conclusions on this topic in this dissertation. We encourage future work on this.

Gender. There is a large variety in gender proportion across EEG studies. The majority of studies included both males and females, though with various male to female ratios (e.g., Loo et al., 2009; Ogrim et al., 2012), or only males (e.g., Clarke et al., 2008), while few studies focussed on females only (e.g., Dupuy et al., 2011). Research suggests sex differences in EEG deviances between males and females with ADHD (for a review, see Dupuy et al., 2013). Even so, studies evaluating only males (Clarke et al., 2008) and only females (Dupuy et al., 2011) have confirmed increased slow wave activity

and/or an elevated TBR in both males and females with ADHD compared to control groups, suggesting that the typically found EEG deviances in ADHD are exhibited in both sexes. As for the current dissertation, the number of females compared to males was somewhat larger than in most other studies. However, this did not impede finding EEG deviances in ADHD when arousal/activation states were manipulated. Moreover, when gender was controlled for in our studies in which no EEG deviances were found between ADHD and typically developing individuals, the group related results did not change. Therefore, we suspect gender not to have played a confounding role in our studies.

Medication effects. Our sample of children and adults with ADHD comprised both individuals who were on and off medication in daily life. Studies examining the acute effects of stimulant medication on EEG activity have described a decrease in theta power (Bresnahan, Barry, Clarke, & Johnstone, 2006; Loo, Teale, & Reite, 1999; Clarke et al., 2003b, 2007) and TBR (Clarke, Barry, Bond, McCarthy, & Selikowitz, 2002b) with medication, resulting in a normalisation of the EEG pattern. Although we are not aware of studies investigating the specific duration of medication effects on EEG activity, throughout our studies, a medication wash-out period of 48 hours was respected in the individuals who used medication in daily life, which is quite restrictive compared to some other studies (e.g., Loo et al., 2010). So far, both studies that incorporate only medication naive patients (e.g., Clarke et al., 2008) and a mixture of individuals who take and do not take medication in daily life (e.g., Shi et al., 2012) have been able to unfold EEG deviances in ADHD. Consequently, we doubt that daily medication use may have confounded our findings. Nevertheless, the role of history of stimulant medication deserves further research, since it has been suggested that the long-term use of stimulants may have a normalizing effect on brain structure in ADHD (Castellanos et al., 2002; Pliszka, Lancaster, Liotti, & Semrud-Clikeman, 2006; Shaw et al., 2009), and hence raises the question if there are possible analogous long-term effects associated with medication use on brain functioning in terms of quantitative EEG as well.

EEG defined subgroups? Although group comparisons show that individuals with ADHD significantly differ from controls on a behavioural and neuropsychological level, there is also a substantial interindividual variability in ADHD (Purper-Ouakil, Ramoz, Lepagnol-Bestel, Gorwood, & Simonnea, 2011). This may probably also apply to EEG activity. Indeed, a few studies have identified several distinct EEG profiles within the disorder (Arns, Gunkelman, Breteler, & Spronk, 2008; Chabot, Orgill, Crawford, Harris, & Serfontein, 1999; Chabot & Serfontein, 1996; Clarke et al., 2011a). In broad outline, EEG-defined groups in ADHD that have been reported throughout the literature are characterised by (a) elevated theta activity (Arns et al., 2008; Chabot et al., 1999) with deficiencies of alpha and beta power (Clarke et al., 2011a), (b) excess beta activity (Arns et al., 2008; Chabot & Serfontein, 1996; Clarke et al., 2011a), (c) elevated alpha activity (Arns et al., 2008; Clarke et al., 2011a), (d) elevated slow wave with less fast wave activity (Clarke et al., 2011a) and (d) low voltage EEG (Arns et al., 2008). While it is possible that EEG heterogeneity characterised our ADHD samples and confined finding significant group differences in certain conditions, the limited sample sizes in the current dissertation did not allow us to investigate the stratification of EEG subgroups.

Differences in topographic distribution of EEG activity in ADHD

In children, yet not in adults, indications were found for a different topographical distribution of EEG activity in ADHD. Consistent differential topographical organisation appeared across conditions before and after cognitive effort (chapter 3) and across conditions with eyes closed and eyes open (chapter 4). In chapter 3, theta and alpha power at the midline were higher than at the lateral sites in the control group, whereas this effect was not detected in the ADHD group. Further, a steeper decrease in midline beta power compared to lateral sites was detected in children with ADHD but not in control children. As for chapter 4, higher midline than lateral power was detected in the delta and theta frequency bands in the control group, yet not in the ADHD group. Also, a

steeper increase from anterior to posterior sites was observed in alpha power across conditions in the control children compared to the children with ADHD. Importantly, this effect was did not result from the children with ADHD incidentally opening the eyes during the recordings, while an experimenter monitored the children during the experiment. As can be seen, the group differences in topographical distribution of EEG activity were not the same in chapter 3 and chapter 4, except for the clearer midline distribution of theta power in the control group compared to the ADHD group. As the participants of those studies largely overlapped, different samples may not serve as an explanation for this inconsistency. Altogether, this also questions the stability of deviances related to topographical organisation of EEG activity in ADHD.

As for the observed midline distribution in delta, theta and alpha power in typically developing children, this is in accord with existing literature (Clarke, Barry, McCarthy, & Selikowitz, 2001b). Whereas a more equivalent distribution of EEG activity across the lateral plane in ADHD has not been demonstrated in other studies, still there are some indications for more deviance between groups at midline than lateral regions in delta and theta power (e.g., Clarke et al., 1998). Regarding alpha power, our findings are in line with findings of greater differences between groups in posterior compared to frontal sites, although other studies in this respect additionally point out that alpha power in ADHD is lower than in controls (see Barry & Clarke, 2009, for a review).

While the exact significance of variations in topographical distribution remains unclear, divergence in ADHD may reflect different underlying neural communication or dysfunction in distributed network organization (for a review, see Konrad & Eickhoff, 2010). As group differences regarding distribution of EEG activity were only found in the child groups we investigated, the question can be raised whether developmental aspects contribute to these findings.

EEG-based classification of ADHD

In chapter 2, it was established that simple spectral EEG parameters were not sufficient to determine the diagnostic status of children and adults. Our overall accuracy rates below 57% align with recent documents, that also demonstrated inadequacy of EEG based classification (Liechti et al., 2013; Ogrim et al., 2012) but contrast with earlier findings of accuracy rates up to 90% (Monastra et al., 2001; Snyder et al., 2008). Given that the ADHD group was not found to differ in EEG activity from the control group, the failure to successfully classify individuals was actually not surprising. However, when analyses were repeated in ADHD-I only, in which deviances in TBR and relative beta power were found, accuracy rates did not enlarge sufficiently.

For the purpose of this discussion, some additional classification analyses were performed in the conditions in which a clear distinction was found between groups, namely during noise exposure and performance of a 2-choice reaction time task in the adult samples. Only the EEG parameters that were found to differ between groups (i.e., midline theta, beta power) were analyzed, resulting in a group classification accuracy of approximately 70% for all measures. These values are still far below the accuracy rates of the abovementioned studies of Monastra and Snyder and are insufficient for clinical diagnostic purposes as they point out that still 3 individuals out of 10 would receive a misclassification, which is unacceptable in clinical practice.

Relationship between EEG parameters and behavioural symptoms of ADHD

Although there are numerous studies investigating EEG activity in ADHD, remarkably few of them have assessed relationships between EEG measures and behavioural symptoms of ADHD. As for theta power, this parameter has sometimes been reported to correlate positively with inattention (Koehler et al., 2009; Ogrim et al., 2012) and once a negative association of this parameter with hyperactivity/impulsivity

was found (Ogrim et al., 2012). Regarding beta power, a positive correlation with inattention has been documented (Ogrim et al., 2012). Further, an inverse relation between TBR and ADHD (van Dongen-Boomsma et al., 2010) and inattention (Loo et al., 2013) has been reported, but otherwise, TBR has also been found to correlate positively with symptoms of inattention (Loo et al., 2013). However, not all studies could identify significant correlations between EEG and ADHD symptomatology after correcting for multiple testing (Swartwood et al., 1998).

Although not reported in the separate chapters of this dissertation, we also performed correlation analyses between EEG parameters and behavioural symptoms of ADHD in our child as well as adult samples. These analyses yielded no consistent correlation patterns between EEG and ADHD symptoms, neither in children, nor in adults.

In all, these findings put into question a consistent interrelationship between simple quantitative EEG parameters and ADHD symptoms.

IMPLICATIONS OF THE RESEARCH FINDINGS

Theoretical and methodological implications

The findings of the present dissertation do not support a transient maturational lag underlying EEG abnormalities, as similar deviances in TBR and beta power were detected in children and adults with ADHD-I. Also, no EEG deviances were found in ADHD when high demands were placed on top-down control, arguing against the model that puts forward reduced cortical control over subcortical structures in ADHD. Together with the recurrent findings of altered EEG responses to manipulations of energetic state, our findings suggest that EEG deviances in ADHD are most likely to be associated with deficiencies in arousal/activation mechanisms. Hence, the results most

closely fit with the EEG-based accounts that emphasize impaired arousal or activation in ADHD. Yet, they add to these models by the notion that EEG deviances are not related to fixed states of underarousal or underactivation in ADHD but are to be regarded from a more dynamic perspective.

Our findings of aberrant EEG activity in ADHD during slow event rates are in agreement with the state regulation account of ADHD, which postulates that individuals with ADHD have difficulties with regulating their energetic state in suboptimal conditions, possibly resulting from impaired extra effort allocation (Sergeant, 2005; van der Meere, 2005). Yet, our findings also appear to suggest deficiencies in modulating energetic state in conditions which act through bottom-up modulation of arousal systems (i.e., eye opening, noise exposure). Although tentative, this may lead to the suggestion that not only top-down but also bottom-up modulation of energetic state in ADHD may be deviant, which would extent the state regulation account.

Our results regarding the effects of noise on EEG activity appear to challenge the optimal stimulation theory (Zentall & Zentall, 1983) and the moderate brain arousal model (Sikström & Söderlund, 2007) of ADHD. Both theories postulate that individuals with ADHD are underaroused, which can be overcome by environmental stimulation. However, in contrast to the predictions of the models, altered EEG activity was not found in the baseline measurement but in the EEG evaluation with stimulation.

From a methodological perspective, the data of this dissertation show that it is of importance to incorporate a large number of electrodes when investigating EEG activity in ADHD. This offers the opportunity to compare widespread cortical activity and thus map differences in topographical distribution in ADHD.

Clinical implications

Diagnostic use of EEG. In July 2013, the U.S. Food and Drug Administration approved the marketing of the Neuropsychiatric EEG-Based Assessment Aid System, which is a medical device that registers TBR in order to assist in assessing ADHD in children and adolescents. It was argued that, when using the device in combination with a complete medical and psychological examination, the accuracy in diagnosing ADHD would largely improve[1]. In light of the findings of the present dissertation, this development is quite worrying. In order to consider TBR as a reliable biomarker for ADHD, this deviance should be a hallmark for all patients and should be stable across different conditions. This was not confirmed by our findings. As a matter of fact, in general little evidence was found for an increased TBR characterising the whole group of ADHD patients, not even when state-related factors were taken into account. Despite the fact that our results confirmed that an elevated TBR might be characteristic for a subgroup of patients, using this parameter to classify those individuals as persons with ADHD proved insufficient, as denoted in the second chapter. Likewise, findings in the separate theta and beta frequency bands did not indicate that those EEG parameters were able to reliably categorize individuals according to their diagnostic status. Hence, EEG-based classification of ADHD is not only challenged by the state-dependent nature of EEG deviances but also by the heterogeneity in ADHD. Moreover, the practice of evaluating EEG activity at only one single place on the scalp (i.e., the vertex), as is done by the Neuropsychiatric EEG-Based Assessment Aid System, runs counter a lot of evidence, including the data presented in this dissertation, which denotes the importance of addressing widespread EEG activity to distinguish individuals with ADHD from typically developing individuals. Also, so far little is known on the specificity of EEG

[1] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm360811.htm

deviances for ADHD. Hence, the utility of simple quantitative EEG measures as a(n additional) diagnostic tool in ADHD should be questioned.

Prognostic use of EEG. Recently, the prognostic use of EEG has gained increasing attention because of its potential in guiding treatment allocation (Arns, Conners, & Kraemer, 2013). The gain of this approach compared to the diagnostic use of EEG is that it takes into account the heterogeneity in ADHD. However, it is still an open question how this approach can be integrated with findings of the state-related nature of EEG deviances in ADHD. Perhaps not restricting EEG recording to one single moment and hence recording EEG in several conditions may be of help to overcome this challenge.

Treatment use of EEG. It is widely recognized that intervention in ADHD should be based on a multimodal approach (Graham et al., 2011), in which stimulant medication and behaviour therapy are considered to be the most effective treatment options (Wolraich et al., 2011). However, limitations of these treatments, such as no (sufficient) response to the interventions, absence of long-term effects, side effects and resistance to treatment options (Sonuga-Barke et al., 2013), validate the search for alternative or additional intervention strategies (van Dongen-Boomsa, Vollebregt, Slaats-Willemse, & Buitelaar, 2013). In this respect, EEG-based neurofeedback therapy has been put into focus as a promising treatment option for ADHD (Gevensleben et al., 2014). In neurofeedback training, individuals learn to self-regulate EEG-activity in a desired direction through the technique of operant conditioning (Heinrich, Gevensleben, & Strehl, 2007). Validated by recurrent findings of enhanced theta and reduced beta activity in earlier studies (for a review, see Barry & Clarke, 2009), neurofeedback treatment traditionally focusses on decreasing activity in the theta band and concurrently increasing activity in the beta band or increasing activity of the sensorimotor rhythm (Gevensleben et al., 2014). Yet, recent studies, including the studies described in this dissertation, question the presence of a stable deviant EEG pattern in ADHD, which challenges the rationale of TBR neurofeedback therapy.

Whether or not neurofeedback training is an effective treatment for ADHD falls beyond the scope of the present dissertation. However, from a translational perspective, the findings of the present dissertation may suggest that it might be beneficial for individuals with ADHD to act upon deficiencies in EEG *modulation*. Perhaps this can be addressed by using a bidirectional approach in neurofeedback frequency training, in which participants learn to modulate EEG activity on demand in both directions (i.e., increase and decrease) in order to target difficulties in state regulation (Liechti et al., 2012, 2013).

Given that neurofeedback treatment is still subject to controversies (Loo & Makeig, 2012), carefulness is warranted in providing specific recommendations regarding this intervention. Yet, as our EEG findings in general illustrate that difficulties in ADHD are state and context dependent, perhaps this can also be of guidance for interventions on a behavioural level. In this respect, the findings stress the importance of providing information and specific intervention strategies about the state dependent nature of ADHD in psychoeducational interventions for parents and teachers.

LIMITATION OF THE RESEARCH

Several specific limitations of the studies incorporated in this dissertation were already outlined in each of the preceding chapters or were integrated in the abovementioned considerations. In this section, some additional limitations referring to the dissertation in its totality are discussed.

First, the ADHD groups were community based samples, which may differ from clinical samples, potentially being characterised by more severe impairment (Brassett-Harknett & Butler, 2007). In addition, the individuals of the ADHD groups were relatively well functioning with mean IQs in the upper average range. Also, a large heterogeneity was reflected in the ADHD samples, comprising all three subtypes of ADHD and a variety

of comorbid disorders, which may have played mediating roles on EEG deviances (Loo et al., 2013). Further, although comparable to other studies in the field (e.g., Liechti et al., 2013; Woltering et al., 2012), the sample sizes were small, which may not have afforded sufficient power to detect significant differences between groups in certain conditions or to disclose modest associations between EEG parameters and behavioural symptoms. As we detected divergence in EEG deviances between ADHD subtypes in the combined sample of children and adults, it would have been interesting to investigate this in the other studies as well but this was not possible due to the undersized samples in the separate groups. Furthermore, the moderate sample sizes did not allow to address EEG heterogeneity, which may be implicated in ADHD (e.g., Arns et al., 2008) and may particularly be of importance to investigate for its potential clinical implications. Yet, in this respect, although not always explicitly mentioned in the separate chapters, when no divergence was found between groups in beta or TBR, it was investigated whether this could be accounted for by some participants with ADHD displaying excess beta power, which was not the case.

There was a large variety in timing of EEG measurement across participants throughout the experiments, which may be a confounding factor as EEG is known to be affected by circadian influences (Sannita, 2006). Moreover, fluctuations in manifestation of behavioural symptoms related to impaired arousal regulation are known to be characterised by time-of-day effects, as confirmed by several studies addressing physiological measures of arousal (i.e., heart rate, cortisol level) (Imeraj et al., 2011, 2012). Unfortunately, we were not able to properly control for circadian effects because we were highly dependent on the schedule of the participating children and adults, requiring EEG evaluation outside school or working hours and feasibility of refraining from medication.

While the findings of this dissertation contribute to the understanding of the significance of EEG deviances in ADHD, this remains a difficult issue. Additional

measures tapping hypothesized factors to be associated with EEG parameters (i.e., arousal, activation, fatigue, vigilance, emotion, motivation) would have been helpful in gaining more insights. In this respect, questionnaires and other physiological measures (i.e., skin conductance level, heart rate variability) would have been an assist.

Another factor impeding the interpretation of the results, refers to the large inconsistency in the use of concepts related to energetic state throughout the literature. Across studies, the terms of arousal, activation, alertness and vigilance have been interpreted in different ways and sometimes appear to be used interchangeably (Barry et al., 2009; Oken et al., 2006; Söderlund et al., 2007), which makes it extremely difficult to assign specific terms to the observed effects.

FUTURE DIRECTIONS

The research findings presented in this dissertation revealed new insights into (the significance of) EEG deviances in ADHD and may serve as a guide for further research, which is discussed in this section.

First, our findings indicate that more research is needed on the sources of heterogeneity in ADHD that have potential mediating and/or opposing effects on EEG deviances. The contributing role of subtypes (or presentation specifiers, as defined in the new DSM publication), comorbid disorders such as ODD/CD, and gender to the manifestation of EEG deviances (and their dynamics) should be further explored in studies with sufficient sample sizes. With respect to comorbidities, it is recommended that learning disabilities (i.e., dyslexia, dyscalculia) are also taken into account, as these disorders are highly prevalent in ADHD samples (Biederman, 2005). The use of larger sample sizes would enable to investigate EEG-based subgroups in ADHD.

Regarding the developmental course of EEG deviances in ADHD, longitudinal studies investigating several (closely spaced) time points may enable to delineate

possible non-linear or differential maturation of EEG in ADHD (Doehnert et al., 2010). As it has been argued that remission of ADHD symptoms is underpinned by structural and functional normalization of the cortex (Halperin, & Schulz, 2006; Shaw, Gogtay, & Rapoport, 2010), it would be interesting to investigate whether adults in remission show a convergence towards typical EEG patterns and whether adults with persistent ADHD establish more non-progressive deficits. A cohort that definitely deserves more attention, is the group of adolescents as so far few studies have addressed EEG activity in these youngsters. In this respect, it is highly recommended that future studies investigate widespread cortical activity, given that EEG has been demonstrated to mature differently depending on scalp region (Clarke et al., 2001b).

Using a large amount of electrodes is not only of importance in maturational studies, it should also be considered as a general practice in ADHD research as this enables to detect potential aberrant topographic distribution of EEG activity, which may reflect an impaired organisation of or interaction within brain networks (Woltering et al., 2012). Regarding this, an additional valuable approach would be to evaluate functional connectivity in brain networks, which can be achieved by EEG coherence measurements. Several studies have already denoted aberrant EEG coherence in individuals with ADHD (e.g., Barry et al., 2011; González et al., 2013; Murias, Swanson, & Srinivasan, 2007) and in a recent study, it was claimed that EEG coherence measures are useful as a diagnostic tool in ADHD (Gonzalez et al., 2013).

As the findings of the present dissertation point to deficiencies in regulation or adaptability of arousal/activation in ADHD, it would be interesting to extent the duration of resting EEG recordings as this may offer opportunities to detect declines in arousal/activation over time. In this respect, it is also recommended that future studies take into account circadian influences in EEG deviances, as previous research has shown that EEG (Sanitta, 2006) as well as arousal states in ADHD (Imeraj et al., 2011, 2012) are sensitive to time-of-day effects.

Regarding task-related EEG activity, an interesting approach that may add to the understanding of EEG deviances in ADHD would be to investigate event-related quantitative EEG. Also, it would be valuable to expand analyses with event related potential component measures. For example, reduced P3 amplitudes are generally explained as reflecting a deficiency in effort allocation (e.g., Banaschewski et al., 2005; Johnstone, Watt, & Dimoska, 2010), while decreased lateralized readiness potential (LRP) amplitudes are considered to reflect reduced preparation of motor activity (i.e., activation) (Bozorgpour, Klorman, & Gift, 2013).

Another promising area for future research is to extend work on the effects of noise on EEG by evaluating this manipulation during task execution, as this may provide further insights into the underlying mechanisms accounting for possible beneficial effects of noise during cognitive effort. With respect to noise, future studies incorporating several levels of noise could test the hypothesis of an inverted U relationship between noise intensity and performance (Söderlund et al., 2007). It is possible that a different intensity level of noise produce different effects on EEG and/or behaviour and that this interferes with diagnostic status, as predicted by the moderate brain arousal model (Sikström & Söderlund, 2007).

To increase knowledge on the significance of EEG deviances in ADHD, it is recommended that future studies incorporate additional measures. For instance, questionnaires and other physiological measures such as skin conductance level or heart rate variability could assist.

FINAL CONCLUSION

The aim of the present dissertation was to increase knowledge on (the functional significance of) EEG deviances in ADHD. The findings provide support for aberrant EEG activity in ADHD, however, they point out that EEG deviances are not to be considered

as core, fixed characteristics but are to be regarded from a contextual and state dependent perspective. This adds to a myriad of studies on behavioural symptoms and cognitive performance, also showing that contextual and state features are implicated in the manifestation of deficits in ADHD.

Our findings indicate that EEG deviances in ADHD are most pronounced in situations in which arousal and activation, which both refer to energetic states of an individual, are manipulated. It was denoted that individuals with ADHD show suppressed theta attenuation in arousal enhancing procedures (i.e., eyes opening, exposure to noise) and exhibit elevated theta power in situations that evoke low activation (i.e., slow event rate). Less reduction of alpha power was also observed in ADHD, be it only with eye opening. Further, enhanced beta power was found in individuals with ADHD during low activation, which was interpreted as an increase in effort allocation to compensate for the underactivation.

Altogether, the findings may indicate a deficiency in brain state regulation or adaptation in ADHD associated with energetic state. In general, this is in accord with the state regulation account of ADHD, putting forward impaired regulation of energetic state related to deficient top-down modulation of energetic systems. Yet, the current findings may extend this account, by suggesting that bottom-up regulation of energetic state in ADHD may be deviant as well.

Besides the state and context dependent nature of EEG deviances in ADHD, it should also be noted that heterogeneity in ADHD plays a role in EEG abnormalities. In specific, subtypes and comorbid disorders contribute to EEG deviances in ADHD.

The results have important clinical implications. First, they indicate that it is not feasible to use simple EEG measures as a (supplementary) diagnostic tool. Second, they may help in creating better interventions or neurofeedback methods for ADHD.

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NEDERLANDSTALIGE SAMENVATTING

INLEIDING

Aandachtstekortstoornis met hyperactiviteit

Aandachtstekortstoornis met hyperactiviteit (attention-deficit/hyperactivity disorder, ADHD) is een ontwikkelingsstoornis die wereldwijd ongeveer 5 tot 7% van de bevolking treft (Willcutt, 2012). ADHD begint in de kindertijd en houdt vaak levenslang aan, hoewel de typerende symptomen een leeftijdsspecifiek karakter vertonen. De stoornis wordt gekenmerkt door aandachtsmoeilijkheden en/of hyperactieve/impulsieve gedragingen die ongepast zijn voor het ontwikkelingsniveau en een negatieve impact hebben op verschillende levensdomeinen. Het klinisch beeld van ADHD kan sterk verschillen tussen personen: sommigen hebben vooral aandachtsmoeilijkheden, terwijl anderen voornamelijk hyperactief/impulsief gedrag vertonen of te kampen hebben met een combinatie van beide probleemdimensies (American Psychiatric Association, 2013). De symptomen zijn vaak meer uitgesproken in situaties waarin hoge eisen worden gesteld aan zelfregulatie, motivatie en informatieverwerking (Imeraj et al., 2013). Een aanzienlijk aantal personen met ADHD heeft één of meerdere bijkomende stoornissen, zoals een oppositioneel opstandige gedragsstoornis, antisociale gedragsstoornis, stemmingsstoornis, angststoornis of leerstoornis (Biederman, 2005).

Etiologie van ADHD

Tot op heden is nog niet volledig duidelijk wat ADHD precies veroorzaakt en in stand houdt. Onderzoek wijst op een belangrijke genetische component maar ook omgevingsfactoren kunnen een risicofactor vormen. Daarnaast zijn verschillende

afwijkingen gevonden in de hersenstructuur en -werking van personen met ADHD (Cortese, 2012).

In de voorbije decennia werden verschillende neuropsychologische theorieën ontwikkeld om de symptomen van ADHD te verklaren. In de "executieve disfunctie theorie" (Barkley, 1997) wordt verondersteld dat ADHD symptomen het gevolg zijn van een primair inhibitieprobleem, wat op zijn beurt andere domeinen van het executief functioneren verstoort. Andere theorieën benadrukken meer het dynamische en contextuele karakter van ADHD. Zo stelt de "aversie voor uitstel theorie" dat een intolerantie voor uitstel en wachtperiodes aan de basis ligt van ADHD symptomen (Sonuga-Barke, Taylor, Sembi, & Smith, 1992), terwijl het "toestandsregulatie model" aanvoert dat personen met ADHD moeilijkheden hebben om hun interne energetische toestand aan te passen aan veranderende omgevingseisen (Sergeant, 2005; van der Meere, 2005). In tegenstelling tot de voorgaande theorieën, waar de klemtoon telkens ligt op één onderliggend deficit, gaat men er de laatste jaren steeds meer van uit dat een combinatie van factoren ten grondslag ligt aan ADHD (Nigg, 2005; Sonuga-Barke, Bitsakou, & Thompson, 2010).

Elektro-encefalografische afwijkingen bij ADHD

Om het de hersenwerking van personen met ADHD in kaart te brengen, wordt vaak gebruik gemaakt van elektro-encefalografie (EEG). EEG meet de elektrische activiteit van de hersenen en verschaft informatie over de toestand waarin een persoon zich bevindt. De meest consistente bevindingen bij personen met ADHD tijdens rustcondities met gesloten en open ogen, zijn een verhoogde activiteit in de theta band en een toegenomen theta/beta ratio (TBR) (Barry & Clarke, 2009; Barry, Clarke, & Johnstone, 2003). Verschillende studies konden deze afwijkingen echter niet terugvinden, wat de robuustheid ervan in vraag stelt (Liechti et al., 2013; Poil et al., 2014). Bovendien hebben een aantal recente studies uitgewezen dat deze

elektrofysiologische vertraging bij slechts 20 tot 60% van de personen met ADHD voorkomt (Arns, Drinkenburg, & Kenemans, 2012; Clarke et al., 2011; Ogrim, Kropotov, & Hestad, 2012) en werd bij sommigen zelfs een verlaagde theta power (Clarke et al., 2011) of TBR (Loo et al., 2013) vastgesteld. Wat betreft de andere frequentiebanden lopen de onderzoeksresultaten nog meer uiteen. Voor zowel alfa als beta power werden tot op heden zowel afwijkingen in beide richtingen als een normaal activiteitspatroon gerapporteerd bij personen met ADHD (Dupuy, Clarke, Barry, McCarthy, & Selikowitz, 2011; Koehler et al., 2009; Liechti et al., 2013; Loo et al., 2010; Shi et al., 2012).

Tijdens het uitvoeren van taken worden vaak gelijkaardige afwijkingen in theta en TBR vastgesteld als tijdens rustsituaties (El-Sayed, Larsson, Persson, & Rydelius, 2002; Monastra et al., 1999), hoewel niet alle studies dit bevestigen (Nazari, Wallois, Aarabi, & Berquin, 2011; Swartwood, Swartwood, Lubar, & Timmermann, 2003). Afwijkende alfa activiteit wordt ook regelmatig teruggevonden bij personen met ADHD tijdens taakuitvoering (Loo et al., 2009; Swartwood et al., 2003; White, Hutchens, & Lubar, 2005).

Verklaringen voor de EEG-afwijkingen bij ADHD

Hoewel verschillende studies verhoogde theta power en/of TBR rapporteren bij personen met ADHD, blijft er onduidelijkheid bestaan over de betekenis van deze afwijkingen. Doorheen de literatuur worden hier een aantal mogelijke interpretaties aan gegeven.

Een eerste theorie interpreteert de afwijkingen als een vertraging in de corticale ontwikkeling, gezien een normaal ontwikkelingsverloop gekenmerkt wordt door een afname van theta power en TBR (Mann, Lubar, Zimmerman, Miller, & Muenchen, 1992; Satterfield, Schell, Backs, & Hidaka, 1984). De onderarousal theorie stelt dat verhoogde theta en TBR veroorzaakt worden door een gebrek aan corticale arousal (Lubar, 1991).

Meer recent schrijft men de vaak gevonden EEG-afwijkingen toe aan een activatieprobleem (Barry, Clarke, Johnstone, McCarthy, & Selikowitz, 2009; Clarke et al., 2013). Tot slot wordt een verhoogde TBR ook gerelateerd aan verminderde corticale controle over subcorticale structuren (Schutter, Leitner, Kenemans, & van Honk, 2006) en wordt de afwijking bijgevolg geïnterpreteerd als de weerspiegeling van een inhibitieprobleem (Putman, van Peer, Maimari, & van der Werff, 2010).

Mogelijke verklaringen voor inconsistente EEG-bevindingen bij ADHD

Niettegenstaande een verhoogde theta power en TBR vaak gerapporteerd worden bij personen met ADHD, neemt het aantal studies waarin deze afwijkingen niet worden teruggevonden stelselmatig toe.

Dit zou vooreerst kunnen te wijten zijn aan het heterogene klinische beeld dat personen met ADHD vertonen. In dit verband rapporteren sommige onderzoekers EEG-verschillen tussen personen met het inattentieve subtype van ADHD en gecombineerde subtype van ADHD (Dupuy et al., 2011; Loo et al., 2010). Er is ook een mogelijk interfererend effect van bijkomende oppositioneel opstandige (ODD) en antisociale (CD) gedragsstoornissen op het EEG van personen met ADHD, ofschoon onderzoek daarover tot nu toe geen eensluidende resultaten opleverde (Clarke, Barry, McCarthy, & Selikowitz, 2002; Loo et al., 2013). Verder wordt gesuggereerd dat EEG-afwijkingen verschillen tussen mannen en vrouwen met ADHD (Dupuy, Barry, Clarke, McCarthy, & Selikowitz, 2013), hoewel de typisch verhoogde theta en TBR doorgaans bij beide geslachten teruggevonden wordt.

Niettegenstaande hier nog geen systematisch onderzoek naar gevoerd werd, lijkt het er ook op dat het optreden van EEG-afwijkingen bij personen met ADHD context- of toestandsafhankelijk is. Zo werd bijvoorbeeld meermaals gevonden dat personen met ADHD meer afwijkingen vertonen in een rustconditie met gesloten ogen dan in een rustconditie met open ogen (Lansbergen, Arns, van Dongen-Boomsma, Spronk, &

Buitelaar, 2011; Loo et al., 2013). Ook de overgang tussen het openen en sluiten van de ogen blijkt anders te verlopen bij personen met ADHD (Fonseca, Tedrus, Bianchini, & Silva, 2013; Liechti et al., 2013; Loo et al., 2010; Woltering, Jung, Liu, & Tannock, 2012), evenals de transitie tussen rust- en taakcondities (Loo et al., 2009; Nazari et al., 2011). Verder zijn EEG-afwijkingen bij personen met ADHD tijdens het uitvoeren van taken sterk taakafhankelijk (Swartwoord et al., 2003; White et al., 2005).

DOELSTELLINGEN VAN HET DOCTORAATSONDERZOEK

Het hoofddoel van dit proefschrift was om de stabiliteit van EEG-afwijkingen en de invloed van dynamische (contextuele, toestandsgerelateerde) factoren op het EEG-profiel van personen met ADHD in kaart te brengen. Een tweede doel was om meer inzicht te krijgen in de functionele betekenis van afwijkende EEG-activiteit bij personen met ADHD. EEG-gebaseerde modellen hebben verhoogde theta power en TBR bij ADHD geïnterpreteerd als een vertraagde corticale ontwikkeling, een gebrek aan corticale arousal, activatieproblemen, of een verminderde executieve top-down controle. Deze hypotheses werden onderzocht en geïntegreerd met inzichten uit diverse invloedrijke neuropsychologische modellen van ADHD.

OVERZICHT EN BESPREKING VAN DE BELANGRIJKSTE ONDERZOEKSRESULTATEN

Stabiliteit van EEG-afwijkingen bij ADHD

Doorheen het proefschrift werden bij zowel kinderen als volwassenen met ADHD het vaakst EEG-afwijkingen vastgesteld in de theta frequentieband. Niettemin was dit geen robuust gegeven en werden in bepaalde condities ook afwijkingen in alfa en beta activiteit waargenomen. In één studie werd een verhoogde TBR opgemerkt bij personen

met ADHD, maar dan enkel bij de onderzoeksparticipanten met het inattentieve subtype.

Verder werden verschillen waargenomen in de topografische distributie van EEG-activiteit tussen kinderen met ADHD en controlekinderen. Ook dit was echter geen consistent gegeven over de studies heen.

Dynamische invloeden op EEG-afwijkingen bij ADHD

Corticale ontwikkelingsvertraging. In hoofdstuk 2 werd onderzocht of mogelijke EEG-afwijkingen bij personen met ADHD verklaard kunnen worden door een corticale ontwikkelingsvertraging (Satterfield et al., 1984). Hiertoe werd de EEG-activiteit van kinderen en volwassenen met en zonder ADHD geanalyseerd tijdens een rustconditie met gesloten ogen. Over beide leeftijdsgroepen heen werden een verhoogde TBR en verminderde relatieve beta power waargenomen bij personen met ADHD, zij het enkel bij de onderzoeksparticipanten met het inattentieve subtype. Deze resultaten suggereren dat EEG-afwijkingen stabiel zijn over de gehele levensloop en vormen bijgevolg geen ondersteuning voor de hypothese van een ontwikkelingsvertraging bij personen met ADHD die wordt ingehaald in de volwassenheid. Enige voorzichtigheid is echter geboden bij de interpretatie van de resultaten door de cross-sectionele aard van het onderzoek.

De invloed van cognitieve inspanning op rust-EEG. In hoofdstuk 3 werd de impact van cognitieve inspanning op een rust-EEG met gesloten ogen nagegaan door de EEG-activiteit van kinderen met en zonder ADHD te evalueren vóór en na het uitvoeren van cognitieve taken. Hoewel er een duidelijke invloed van het uitvoeren van de taken merkbaar was op het EEG-patroon, was deze van dezelfde aard bij de kinderen met en zonder ADHD en werd geen abnormale EEG-(re)activiteit vastgesteld bij kinderen met

ADHD. De intermediaire cognitieve inspanning op zich bleek dus geen versterkende of afzwakkende factor te zijn voor afwijkende EEG-activiteit in rust bij kinderen met ADHD.

De invloed van arousal. In het vierde en vijfde hoofdstuk werd dieper ingegaan op de hypothese van een verminderde arousal als verklaring voor EEG-afwijkingen bij personen met ADHD (Lubar, 1991).

In hoofdstuk 4 werd de EEG-activiteit van kinderen met en zonder ADHD vergeleken tijdens rustcondities met gesloten en open ogen. Gezien het openen van de ogen gepaard gaat met een arousalverhoging (Barry, Clarke, Johnstone, Magee, & Rushby, 2007; Hüfner et al., 2009), representeren deze onderzoekscondities twee verschillende toestanden van arousal. In geen enkele conditie werd abnormale EEG-activiteit vastgesteld bij kinderen met ADHD. Het openen van de ogen resulteerde bij de ADHD groep (zonder bijkomende ODD/CD) echter wel in een kleinere daling van posterieure alfa en theta activiteit dan bij de controlegroep.

In hoofdstuk 5 werd de mogelijkheid van een verlaagd arousalniveau verder onderzocht en werd het effect van externe achtergrondruis op het EEG van volwassenen met ADHD nagegaan (Sikström & Söderlund, 2007). In deze studie werd de EEG-activiteit van een groep personen met ADHD en groep typisch ontwikkelende personen vergeleken tijdens rustcondities met gesloten ogen zonder en met achtergrondruis. Het EEG-profiel van volwassenen met ADHD verschilde niet van dat van typisch ontwikkelende volwassenen in de baseline rustconditie. Niettemin werd een kleinere afname in theta activiteit opgemerkt bij volwassenen met ADHD bij het aanbieden van ruis na een baselinemeting. Dit suggereert een andere adaptatie aan ruis bij de ADHD groep dan bij de controlegroep.

De invloed van activatie. In hoofdstuk 6 werd onderzocht of een activatieprobleem aan de basis kan liggen van EEG-afwijkingen bij ADHD (Barry et al., 2009). Hiertoe werd de EEG-activiteit van volwassenen geëvalueerd tijdens het

uitvoeren van een trage eenvoudige perceptuele beslissingstaak, die een toestand van lage activatie induceerde. Volwassenen met ADHD reageerden trager en meer variabel en hadden de neiging om meer fouten te maken dan controlevolwassenen, wat in overeenstemming is met literatuur die slechtere prestaties bij ADHD tijdens trage taakcondities rapporteert (Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012, voor een meta-analyse). Deze groepsverschillen werden ook op EEG-niveau gereflecteerd, waarbij de volwassenen met ADHD een verhoogde theta en beta activiteit vertoonden.

Verminderde top-down controle. Om de hypothese van een onderliggend inhibitieprobleem te onderzoeken (Putman et al., 2010), werd het EEG bij volwassenen geanalyseerd tijdens de uitvoering van een flanker taak, die aandachtsgerichte top-down controle vereist. Er werd een tragere reactietijd waargenomen bij volwassenen met ADHD maar de ADHD groep vertoonde een gelijkaardige executieve controle als de controlegroep. Dit is een niet geheel onverwacht resultaat, gezien onderzoek heeft aangetoond dat problemen in het executief functioneren niet bij alle volwassenen met ADHD voorkomen (Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005) en prestaties op taken die executieve functies nagaan sterk kunnen variëren tussen personen met ADHD (Nigg et al., 2005). Ook op vlak van EEG-activiteit werden geen groepsverschillen waargenomen tijdens het uitvoeren van deze taak, hoewel er -zoals hierboven beschreven- bij dezelfde volwassenen wel EEG-groepsverschillen werden vastgesteld tijdens het uitvoeren van de trage perceptuele beslissingstaak. Dit alles biedt weinig ondersteuning voor de hypothese dat EEG-afwijkingen een weerspiegeling vormen van een inhibitieprobleem bij personen met ADHD.

Conclusies met betrekking tot de dynamische invloeden op EEG-afwijkingen bij ADHD. Samenvattend kan geconcludeerd worden dat het EEG-profiel van personen met ADHD verschilde van dit van typisch ontwikkelende personen in situaties waarin arousal- en activatieniveaus werden gemanipuleerd.

Niettegenstaande personen met ADHD geen afwijkende EEG-activiteit lieten zien tijdens condities waarin een laag niveau van arousal verondersteld werd, vertoonden ze wel een verminderde theta (en in mindere mate alfa) reactiviteit tijdens arousalverhogende procedures. Hoewel een aantal studies heeft aangetoond dat theta power wel verandert in arousal opwekkende situaties zoals het openen van de ogen (Barry et al., 2007; Boytsova & Danko, 2010) of het toedienen van cafeïne (Gilbert, Dibb, Plath, & Hiyane, 2000), is toch enige voorzichtigheid geboden met het interpreteren van theta activiteit als een maat voor arousal. Theta power blijkt namelijk, in tegenstelling tot alfa power, geen goede samenhang te vertonen met huidgeleidingsactiviteit (Dupuy, Clarke, Barry, Selikowitz, & McCarthy, 2014), die beschouwd wordt als een betrouwbare indicator voor autonome arousal (Critchley, 2002). De observatie van een verhoogde theta power bij personen met ADHD tijdens een toestand van lage activatie sluit aan bij het theoretische model dat stelt dat een activatieprobleem aan deze afwijking ten grondslag ligt (Barry et al., 2009). De onderzoeksresultaten suggereren echter dat dit model kan uitgebreid worden met de idee dat verminderde activatie geen basiskenmerk is van personen met ADHD en afhankelijk is van omgevingsfactoren. Globaal genomen wordt verhoogde activiteit in de theta band van oudsher geassocieerd met een toestand van verminderde alertheid (Barwick, Arnett, & Slobounov, 2012; Oken, Salinsky, & Elsas, 2006). In dit opzicht kunnen de huidige bevindingen mogelijk aangeven dat personen met ADHD moeilijkheden hebben met de overgang van een minder alerte naar een meer alerte toestand (hoofdstuk 4 en hoofdstuk 5), en sneller in een toestand van verminderde alertheid verkeren wanneer de omgeving weinig stimulansen biedt (hoofdstuk 6). Niettemin lijken personen met ADHD wel te proberen om te compenseren voor een laag activatieniveau door extra effort allocatie (beta activiteit) (Fischer, Langner, Birbaumer, & Brocke, 2008; Smit, Droogleever Fortuyn, Eling, & Coenen, 2005).

Vanuit dit interpretatiekader is het mogelijk dat er tijdens het uitvoeren van de flanker taak geen EEG-afwijkingen bij personen met ADHD werden waargenomen doordat de aanbiedingssnelheid van de stimuli geen daling in het activatieniveau van de deelnemers teweegbracht. Dit doet ook de vraag rijzen of er na het uitvoeren van taken die een laag activatieniveau opwekken bij kinderen, andere EEG-resultaten zouden gevonden zijn als na de cognitieve taken die afgenomen werden in hoofdstuk 3.

Heterogeniteit bij personen met ADHD

Naast het feit dat EEG-afwijkingen bij ADHD context- en toestandsafhankelijk blijken te zijn, laten de onderzoeksresultaten zien dat deze ook worden beïnvloed door verschillende mediërende factoren die samenhangen met ADHD, zoals ADHD subtypes en bijkomende stoornissen. In hoofdstuk 2 werd namelijk een meer afwijkend EEG-patroon waargenomen bij personen met het inattentieve subtype dan bij personen met het gecombineerde subtype. Dit was niet toe te schrijven aan de ernst van de aandachtsproblemen. Wegens de kleine steekproeven was het niet mogelijk om de invloed van ADHD subtypes te bestuderen in de andere hoofdstukken. De onderzoeksbevindingen wijzen er ook op dat bijkomende ODD/CD een invloed kan hebben op EEG-afwijkingen bij kinderen met ADHD. In hoofdstuk 4 werd bij het openen van de ogen enkel een abnormale EEG-reactiviteit gevonden wanneer de kinderen met een bijkomende gedragsstoornis uitgesloten werden van de analyses. Niettemin werd geen invloed van deze comorbiditeit vastgesteld op het rust-EEG voor en na cognitieve inspanning (hoofdstuk 5). In aanmerking genomen dat slechts een aantal kinderen een bijkomende gedragsstoornis hadden en er geen rechtstreekse vergelijking kon gemaakt worden tussen kinderen met ADHD en kinderen met ADHD en een bijkomende ODD/CD, zijn conclusies hieromtrent ietwat voorbarig. Meer onderzoek is nodig om de rol van subtypes en bijkomende gedragsstoornissen bij het optreden van EEG-afwijkingen verder te bestuderen.

ADHD-classificatie op basis van het EEG

In hoofdstuk 2 werd de bruikbaarheid van het EEG nagegaan bij het stellen van een ADHD diagnose. Geen enkele van de bestudeerde EEG-parameters bleek de diagnostische status van een persoon met voldoende accuraatheid te kunnen aangeven. Gezien de globale resultaten van dit proefschrift aantonen dat EEG-afwijkingen bij ADHD een dynamisch karakter vertonen en tevens kunnen worden beïnvloed door factoren die samenhangen met de heterogeniteit van de stoornis, is dit geen onverwacht gegeven.

IMPLICATIES VAN HET ONDERZOEK

Theoretische implicaties

Wanneer de onderzoeksresultaten bekeken worden in het licht van bestaande neuropsychologische modellen van ADHD die problemen toeschrijven aan de energetische toestand van personen, lijken deze niet in lijn te liggen met de voorspellingen van de optimale stimulatie theorie (Zentall & Zentall, 1983) en het moderate brain arousal model (Sikström & Söderlund, 2007). Deze gaan namelijk uit van een gebrek aan arousal bij personen met ADHD, dat mogelijk kan gecorrigeerd worden met omgevingsstimulatie. Er werden in het huidige proefschrift geen EEG-afwijkingen gevonden bij personen met ADHD in condities met een laag arousalniveau, maar de bevindingen wezen wel in de richting van een verminderde adaptatie aan arousalverhogende condities. Samen met de bevindingen dat het EEG bij personen met ADHD afwijkt in een situatie waarin een laag activatieniveau teweeggebracht werd, lijken deze resultaten het nauwst aan te sluiten bij de toestandsregulatie theorie van ADHD (Sergeant, 2005; van der Meere, 2005), die stelt dat personen met ADHD moeilijkheden hebben om hun interne energetische toestand aan te passen aan veranderende omgevingseisen. Daar waar het toestandsregulatie model vooral een

probleem in de top-down regulatie van arousal/activatie benadrukt, lijken de onderzoeksresultaten te indiceren dat er bij personen met ADHD mogelijk ook een probleem is met bottom-up regulatie van de energetische toestand.

Klinische implicaties

De laatste jaren is er een toenemende belangstelling voor het gebruik van kwantitatief EEG bij de diagnosestelling en behandeling van ADHD (Loo & Makeig, 2012).

De onderzoeksresultaten van dit proefschrift laten zien dat het niet opportuun is om simpele kwantitatieve EEG-maten in te zetten als diagnostisch hulpmiddel bij ADHD. Een voorwaarde om EEG-afwijkingen als goede biomarkers voor de stoornis te beschouwen, is namelijk dat deze stabiel en universeel zijn (Thome et al., 2012), wat niet ondersteund wordt door de huidige bevindingen. Bovendien is nog weinig gekend over de specificiteit van de EEG-afwijkingen bij de stoornis, wat ook een bepalende factor is voor de inzetbaarheid van het EEG voor diagnostische doeleinden (Loo & Makeig, 2012).

De onderzoeksbevindingen dagen bijkomend de oorspronkelijke rationale van TBR neurofeedbacktraining bij ADHD uit. Vanuit de regelmatig terugkerende verhoogde theta en verminderde beta activiteit bij personen met ADHD in tal van studies (voor een overzicht, zie Barry & Clarke, 2009), wordt bij deze behandeling via het principe van operante conditionering aangeleerd om activiteit in de theta band te reduceren en tegelijkertijd activiteit in de beta band te verhogen (Gevensleben et al., 2014). De bevindingen van dit proefschrift wijzen echter eerder op een tekortkoming in het adapteren of reguleren van EEG-activiteit dan op de aanwezigheid van een stabiel afwijkend EEG-patroon bij personen met ADHD. Van daaruit is een bidirectionele training van EEG-activiteit, waarin de deelnemers leren om deze activiteit op verzoek zowel te reduceren als te verhogen, misschien meer aangewezen om de problemen met toestandsregulatie op te vangen (Liechti et al., 2012, 2013). Verder onderzoek is nodig om hier meer duidelijkheid in te brengen.

CONCLUSIE

De voornaamste doelstelling van dit proefschrift was om de stabiliteit van en mogelijke dynamische invloeden op afwijkende EEG-activiteit bij personen met ADHD in kaart te brengen. Een tweede doel was om meer inzicht te krijgen in de functionele betekenis van EEG-afwijkingen bij personen met ADHD.

De onderzoeksresultaten bevestigen dat personen met ADHD afwijkende EEG-activiteit vertonen, maar wijzen op het toestands- en contextafhankelijke karakter hiervan. Deze bevindingen vormen een aanvulling op een groot aantal studies die aantonen dat ook de mate waarin de symptomen en cognitieve moeilijkheden die tot uiting komen bij personen met ADHD beïnvloed worden door toestandsgerelateerde en contextuele factoren. De EEG-afwijkingen bij personen met ADHD zijn het meest uitgesproken in situaties waarin arousal- en activatieniveaus, die beide betrekking hebben op de energetische toestand van een individu, worden gemanipuleerd.

Naast het contextafhankelijke karakter van EEG-afwijkingen bij personen met ADHD, blijkt het optreden van deze afwijkingen ook beïnvloed te worden door verschillende factoren die samenhangen met ADHD, zoals de klinische presentatie van de stoornis in subtypes en bijkomende ODD/CD.

De onderzoeksresultaten hebben een aantal belangrijke klinische implicaties. Vooreerst geven ze aan dat het niet aangewezen is om EEG in te zetten als aanvullend diagnostisch hulpmiddel. Ten tweede kunnen de onderzoeksbevindingen een aanzet geven tot de verbetering van bestaande of het ontwikkelen van nieuwe evidence based neurofeedbackmethodes voor ADHD.

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